Frailty, Malnutrition and Heart Failure

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Declaration

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Signed _____Shirley Sze_____ Date _____27.8.2019_____

List of Publications

Original articles

Sze S, Pellicori P, Zhang J, Weston J, Clark AL. Identification of Frailty in Chronic Heart Failure. *JACC Heart Fail* 2019;**7:**291-302.

Sze S, Pellicori P, Zhang J, Clark AL. Malnutrition, congestion and mortality in ambulatory patients with heart failure. *Heart* 2018. doi: 10.1136/heartjnl-2018-313312.

Sze S, Pellicori P, Kazmi S, Rigby A, Cleland JGF, Wong K, Clark AL. Prevalence and Prognostic Significance of Malnutrition Using 3 Scoring Systems Among Outpatients With Heart Failure: A Comparison With Body Mass Index. *JACC Heart Fail* 2018;**6:**476-86.

Sze S, Pellicori P, Kamzi S, Anton A, Clark AL. Effect of beta-adrenergic blockade on weight changes in patients with chronic heart failure. *Int J Cardiol* 2018;**264:**104-12.

Sze S, Zhang J, Pellicori P, Morgan D, Hoye A, Clark AL. Prognostic value of simple frailty and malnutrition screening tools in patients with acute heart failure due to left ventricular systolic dysfunction. *Clin Res Cardiol* 2017;**106**:533-41.

Publications under review:

Sze.S, Pellicori. P, Zhang.J, Weston.J, Clark AL. The prevalence of malnutrition in patients with chronic heart failure. (Am J Clin Nutr)

Sze.S, Pellicori. P, Zhang.J, Weston.J, Clark AL. Frailty predicts mortality and hospitalisation in patients with chronic heart failure. (Eur Heart J)

Sze.S, Pellicori. P, Zhang.J, Weston.J, Clark AL. Malnutrition predicts mortality and hospitalisation in patients with chronic heart failure. (J Am Coll Cardiol)

Editorial

Clark AL, **Sze S.** Impact of Malnutrition Using Geriatric Nutritional Risk Index in Heart Failure with Preserved Ejection Fraction. *JACC Heart Fail* 2019;**7**:676-77.

Abstracts

Sze.S, Pellicori. P, Zhang.J, Weston.J, Clark AL. Frailty evaluation in patients with chronic heart failure - A comparison of screening vs assessment tools. *EJHF Suppl* 2019;21(Suppl. S1)1–2. Doi:10.1002/ejhf.1487

Sze.S, Pellicori. P, Zhang.J, Weston.J, Clark AL. Evaluation of malnutrition using 6 screening tools in patients with chronic heart failure. *EJHF Suppl* 2019;21(Suppl. S1)1–2. Doi:10.1002/ejhf.1487

Sze S, Pellicori P, Kamzi S, Anton A, Clark AL. The effect of beta-adrenergic blockade on weight change and mortality in patients with chronic heart failure. *Eur Heart J Suppl* 2018; 20. Doi: https://doi.org/10.1093/eurheartj/suy011

Sze S, Pellicori P, Zhang J, Clark AL. Malnutrition and its association with congestion in chronic heart failure. *Eur Heart J Suppl* 2018;20. Doi: https://doi.org/10.1093/eurheartj/suy011

Sze S, Pellicori P, Kazmi S, Rigby A, Cleland JGF, Wong K, Clark AL. Nutritional State predicts long term survival in Chronic Heart Failure. *Eur Heart J Suppl 2017; 19.* Doi: https://doi.org/10.1093/eurheartj/sux014

Sze S, Zhang J, Pellicori P, Hoye A, Clark AL. Prognostic value of simple frailty screening tools in patients with acute heart failure. *Eur Heart J Suppl*. 2016; 37. Doi: http://dx.doi.org/10.1093/eurheartj/ehw432

Sze S, Wong KYK, Kazmi S, Rigby A, Clark AL. Nutritional state predicts long-term survival in heart failure. Eur Heart J Suppl 2015;36. Doi: http://dx.doi.org/10.1093/eurheartj/ehv399

List of Presentations at international/ national meetings

Sept 2019	22nd Annual Meeting of the British Geriatrics Society Cardiovascular Section. Poster presentation: *"Prevalence and prognostic significance of frailty in patients with chronic heart failure"*
Aug 2019	European Society of Cardiology International Congress 2019. France. Poster presentation: "*Agreement and prognostic significance of 6 frailty tools in patients with chronic heart failure"*
June 2019	British Cardiovascular Society Annual conference 2019. Manchester. Oral presentation: *"Efficacy of frailty tools in detecting frailty and predicting hospitalisation and mortality in patients with chronic heart failure"*
May 2019	Heart Failure 2019 & World Congress in Acute Heart Failure 2019. Athens. Moderated poster presentations: *"Frailty Evaluation in patients with chronic heart failure – a comparison of screening vs assessment tools"* and *"Evaluation of malnutrition using 6 screening tools in patients with chronic heart failure"*
Nov 2018	21st British Society for Heart Failure Annual Autumn Meeting. London. Oral presentation young investigator award: "*Prevalence and Prognostic Significance of Frailty in patients with Chronic Heart Failure – a comparison of 3 screening versus 3 assessment tools"*
Aug 2018	European Society of Cardiology International Congress 2018. Munich. Poster presentations: *"Malnutrition and its association with congestion in chronic heart failure"* and *"The effect of beta-adrenergic blockade on weight change and mortality in patients with chronic heart failure"*

June 2018	British Cardiovascular Society Annual conference 2018. Manchester. Oral presentation: *"Effect of Beta-adrenergic blockade on weight changes in chronic heart failure patients due to left ventricular systolic dysfunction"*
May 2018	Heart Failure 2018 & World Congress in Acute Heart Failure 2018. Poster presentation: *"The relationship between malnutrition and congestion in chronic heart failure*" and *"The relation between beta-adrenergic blockade and weight changes in patients with chronic heart failure"*
June 2017	British Cardiovascular society Annual conference 2017. Manchester. Moderated poster presentation: "*Prognostic value of simple malnutrition tools in patients with chronic heart failure"*
May 2017	European Society of Cardiology Heart Failure 2017- 4th World Congress on Acute Heart Failure. Rapid fire oral presentation: *"Prognostic value of malnutrition screening tools in patients with chronic heart failure"*
Nov 2016	19th British Society for Heart Failure Annual Autumn Meeting. London. Oral presentation young investigator award: *"The role of frailty and malnutrition screening tools in patients admitted for heart failure"*
Aug 2016	European Society of Cardiology International Congress 2016. Rome. Best poster presentation: *"Prognostic value of simple frailty screening tools in patients with acute heart failure"*
Aug 2015	European Society of Cardiology International Congress 2015. London. Rapid fire oral presentation: *"Nutritional state predicts long-term survival in heart failure"*

List of Awards

2019 "Best of the Best Clinical Abstracts 2019. British Cardiovascular Society. *"The efficacy of frailty tools in detecting frailty and predicting hospitalisation and mortality in patients with chronic heart failure"*

Travel grant for Heart Failure 2019 & World Congress in Acute Heart Failure (€400)

British Junior Cardiologists' Association essay competition 2019. Winner essay: *"Will heart failure become the first cyber specialty?"* (This essay discusses the challenges in implementing digital healthcare in the management of elderly patients with HF)

Corrine Camilleri-Ferrante Prize. Health Education England. (£1000)
Winner presentation: *"What medicine will be like when I retire?"*
(This presentation discusses how medicine will change as a result of the ageing population and its associated global pandemics of chronic diseases including heart failure.)

2018 Young Investigator's Award Runner Up. British Society for Heart Failure. *"Prevalence and Prognostic Significance of Frailty in patients with Chronic Heart Failure – a comparison of 3 screening versus 3 assessment tools"*

Hull York Medical School Postgraduate Researcher of the Year 2018. The prize is awarded to an outstanding postgraduate research student who has the highest achievement in: 1) academic excellence in relation to the stage of research; 2) reach of the researcher's contribution; 3) impact of the research; 4) contribution to postgraduate research environment or society.

Best of the Best Clinical Abstracts 2018. British Cardiovascular Society
"Effect of Beta-adrenergic blockade on weight changes in chronic heart failure patients due to left ventricular systolic dysfunction"

Travel grant for Heart Failure 2018 & World Congress in Acute Heart Failure (€300)

2017 Best Abstract Award 2017. British Cardiovascular Society.
"Prognostic value of simple malnutrition tools in patients with chronic heart failure"

Postgraduate research funding bid. Hull York Medical School & University of Hull. (£550).

European Society of Cardiology Congress Educational Grant (€850)

2016 Young Investigator's Award-Runner Up. British Society for Heart Failure.
"Prognostic value of simple frailty and malnutrition screening tools in patients with acute heart failure"

List of grant application

British Heart Foundation Hope for Hearts Fund: “A holistic patient-centred intervention to improve outcomes of older people living with frailty and chronic heart failure” (£168,397)
[Principal investigator: Dr Shirley Sze. Co-applicants: Professor Iain Squire, Professor Simon Conroy, Professor Carolyn Tarrant, Miss Louise Clayton]

ABSTRACT

Heart failure (HF) is a common medical condition with significant morbidity and mortality. As the population ages, the prevalence of HF increases. Elderly patients with HF have different characteristics compared to younger patients; with increasing co-morbidities and diminished physiological reserves. However, most clinical trials in HF do not include patients who are elderly and management of these patients remain a medical challenge. Frailty and malnutrition appear to be common in elderly patients, but their role in HF management is currently unknown.

This thesis describes a series of studies which examined in detail frailty and malnutrition in patients with HF. I first studied the prevalence of frailty and malnutrition in different populations of HF patients (acute versus chronic HF; HF with reduced versus normal ejection fraction). I then explored the clinical correlates of frailty and malnutrition, focusing on their relation to age, gender, HF symptoms and severity. Next, in order to identify the best tool to measure frailty and malnutrition in patients with HF, I performed comprehensive frailty and malnutrition evaluations using 18 commonly used tools. I compared the agreement, classification performance and prognostic value of screening versus assessment tools; simple versus multi-dimensional tools and combination scores versus single physical or laboratory tests. Finally, I attempted to explore the underlying pathophysiology of frailty and malnutrition by studying their relation to congestion and sympathetic activation.

I found that frailty and malnutrition are common in patients with HF. They correlate with older age, higher co-morbidity burden, worse symptoms and severity of HF. Furthermore, I demonstrated that frailty and malnutrition, regardless of the tool used, are both independent predictors of a worse prognosis. These findings support routine evaluation of frailty and malnutrition in clinical practice when managing patients with HF. Future studies should focus on interventions targeting frailty and malnutrition in patients with HF.

(300 words)

Table of Contents

List of Figures

Chapter 8

Chapter 9

Chapter 10

Chapter 11

Chapter 12

List of Tables

Chapter 4

Chapter 5

Chapter 6

Chapter 7

Chapter 8

Chapter 9

Chapter 10

Chapter 11

Chapter 12

Chapter 13

List of Appendices

Index of Abbreviations

ACEi = Angiotensin converting enzyme inhibitor

ACS = Acute coronary syndrome

AF = Atrial fibrillation

AFN = Acute Frailty Network

AIDS = Acquired immune deficiency syndrome

AKI = Acute kidney injury

ARB = Angiotensin receptor blocker

ARNI = Angiotensin receptor neprilysin inhibitor

AHF = Acute heart failure

BB = Beta-blocker

BMI = Body mass index

BP = Blood pressure

Bpm = Beats per minute

CFS = Clinical frailty scale

CHF = Chronic heart failure

CI = Confidence interval

CLL = Chronic lymphocytic leukaemia

CONUT = Controlling nutritional status

COPD = Chronic obstructive pulmonary disease

CoQ10 = Coenzyme Q10

CVD = Cerebrovascular disease

DFI = Derby frailty index

DI = Deficit index

E/e' = Ratio between early mitral inflow velocity and mitral annular early diastolic velocity

ECG = Electrocardiogram

EFS = Edmonton frailty score

eGFR = Estimated glomerular filtration rate

ESC = European Society of Cardiology

GNRI = Geriatric nutritional risk index

GLS = Global longitudinal strain

Hb = Haemoglobin

HF = Heart failure

HR = Hazard ratio

HeFREF = Heart failure with reduced ejection fraction

HeFNEF = Heart failure with normal ejection fraction

HIV = Human immunodeficiency virus

HTN = hypertension

IHD = Ischaemic heart disease

IQR = Interquartile range

IL = Interleukin

IVC = Inferior vena cava

JVP = Jugular venous pressure

K = Kappa coefficient

LA = Left atrium / left atrial

LAVI = Left atrial volume index

LLR = Log-likelihood ratio

LV = Left ventricular

LVEF = Left ventricular ejection fraction

LVSD = Left ventricular systolic dysfunction

LVESD = Left ventricular end systolic diameter

LVESV = Left ventricular end systolic volume

LVEDD = Left ventricular end diastolic diameter

LVEDV = Left ventricular end diastolic volume

LVH = Left ventricular hypertrophy

LVI = Left ventricular impairment

MI = Myocardial infarction

MNA-SF = Mini nutritional assessment – short form

MRA = Mineralocorticoid receptor antagonist

MUST = Malnutrition universal screening tool

N/A = Not applicable

NHS = National Health Service

NICE = National Institute of Clinical Excellence

NPV = Negative predictive value

NRI = Net reclassification index

NT-proBNP = N-terminal pro brain natriuretic peptide

NYHA = New York Heart Association

PAsP = Pulmonary artery systolic pressure

PPV = Positive predictive value

PUFA = Polyunsaturated fatty acid

PVD = Peripheral vascular disease

QoL = Quality of life

QRS = Q, R and S waves on electrocardiogram

RCT = Randomised controlled trials

RAP = Right atrial pressure

RV = Right ventricle/ right ventricular

RVSD = Right ventricular systolic dysfunction

SD = Standard deviation

SGA = Subjective global assessment

SR = sinus rhythm

TAPSE = Tricuspid annular plane systolic excursion

TIA = Transient ischaemic attack

TR Vmax = Maximal tricuspid regurgitation velocity

TUGT = Timed get up and go test

vs = versus

χ^2 = Chi-square

5MWT = Five meter walk test

Dedication

I dedicate this thesis to my wonderful parents, sister and grandparents who unconditionally supported and encouraged me to pursue my dreams.

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Chapter 1 Heart Failure and the Ageing Population

1.1 Introduction

Advancements in medical care have led to improved quality of life (QoL) and longer average lifespans. The global elderly population of individuals over the age of 60 years is expected to increase from 600 million in the year 2000 to 2 billion by 2050 (1). Managing the ageing population has become the new challenge in medicine. Therapies previously proven to be effective may no longer be applicable to the ageing population. Over the past decade, increasing resources have been used to understand the ageing process, in the hope of improving medical care for elderly patients in our society.

Ageing leads to deterioration in general health and predisposes the individual to a wide spectrum of cardiovascular diseases. Older adults are at higher risk of developing atherosclerosis, atrial fibrillation (AF), left ventricular hypertrophy (LVH) (2), predisposing to myocardial infarction (MI), heart failure (HF) and consequently worse outcomes (3).

1.2 Heart Failure

1.2.1 What is heart failure?

HF is a clinical syndrome caused by a defect in the structure and/or function of the heart, leading to reduction in cardiac output and/or elevation in intra-cardiac pressures at rest or during stress (4, 5). It is the final common pathway of most forms of cardiovascular diseases. Typical symptoms of HF include breathlessness, ankle swelling and fatigue. Typical signs of HF include peripheral oedema, elevated jugular venous pressure (JVP) and lung crackles (5). The New York Heart Association (NYHA) functional classification is commonly used to describe severity of symptoms and exercise intolerance (6).

1.2.2 Types of heart failure

HF can be differentiated by left ventricular ejection fraction (LVEF) into 2 main types: heart failure with reduced ejection fraction (HeFREF) and heart failure with normal ejection fraction (HeFNEF). Such differentiation is important due to differences in demographics, associated co-morbidities, underlying aetiology and response to therapies (7). In the United Kingdom (UK), the most common type of HF is HeFREF, typically defined as LVEF <40%, where there is impaired LV contraction (systolic dysfunction), usually as a result of ischaemic heart disease (IHD). HeFNEF is typically considered when LVEF ≥50%, where there is impaired filling of the left ventricle (diastolic dysfunction), usually as a result of long-standing hypertension (HTN) (4). HeFNEF is typically associated with older age, female sex and AF. HeFNEF is sometimes referred to as "HeFPEF" with P standing for "preserved". The term is potentially misleading as it implies a knowledge of the LVEF prior to symptoms developing. Recently, a third type of HF, heart failure with mid-range ejection fraction (HeFmREF) has emerged. Patients with HeFmREF have LVEF between 40-49% with primarily mild systolic dysfunction but also features of diastolic dysfunction. Patients with HeFmREF have characteristics intermediate between HeFREF and HeFNEF. The European Society of Cardiology (ESC) guidelines for HF suggest that further studies are required to characterise HeFmREF (5).

HF can also be classified as chronic heart failure (CHF), where patients have relatively stable symptoms; or acute heart failure (AHF), where symptoms become severe and require hospitalisation. The typical course of CHF is punctuated intermittently by decompensations into AHF, although optimal HF management might prevent the latter.

1.2.3 Investigations for heart failure

Natriuretic peptides, electrocardiogram (ECG) and echocardiography are essential initial investigations for HF. Natriuretic peptides have high negative predictive values but low positive predictive values; they are useful to rule out HF but not to establish the diagnosis (8). ECG provides information on aetiology (such as LVH and MI) or indications for therapy (such as anticoagulation for AF and cardiac resynchronisation therapy for patients with broad QRS complexes). Echocardiography is the most useful and widely available

bedside test in patients with suspected HF. It provides information on ventricular systolic and diastolic function, wall thickness, chamber volumes, valve function and pulmonary hypertension, which are crucial for establishing a diagnosis and determining appropriate treatment (9).

1.2.4 Prevalence

In the UK, an estimated 900,000 people have HF (10). The prevalence of HF in developed countries ranges between 1-2% in the adult population, increasing to over 10% in adults over 85 years old (11). According to the National Heart Failure Audit, HF contributes to about 5% of all emergency hospital admissions in adults (4). The median age of patients hospitalised with HF was 80 years (4).

1.2.5 Prognosis

HF is associated with a poor prognosis. It contributes to 2% of the total National Health Service (NHS) expenditure (12). Patients with HF suffer marked reduction in mobility and QoL with increased morbidity and mortality. Mortality rates vary depending on age, disease severity and quality of care. Amongst patients admitted with HF, the in-hospital and 1-year mortality rate was 9% and 23% respectively. In-hospital mortality was almost 3 times higher in patients >75 years compared to those ≤ 75 years (4).

1.2.6 Management

Management of HF is dependent on the type of HF (HeFREF vs HeFNEF) and the mode of presentation (AHF vs CHF). Over the past 3 decades, there has been major advancements in the management of patients with CHF with reduced ejection fraction. Disease modifying treatment such as angiotensin converting enzyme inhibitors (ACEi)/ angiotensin receptor blockers (ARB)/ angiotensin receptor–neprilysin inhibitors (ARNI), beta-blockers and mineralocorticoid receptor antagonists (MRA) have been shown to improve symptom control and reduce hospitalisations and mortality (5, 13). They should

be initiated in all patients with HeFREF (4). Patients enrolled in clinical trials who were receiving optimal therapy, have significantly lower 1-year mortality rate compared to the general HF population (<10% vs 23%) (4).

Management of AHF is challenging. The in-hospital and 30-day mortality rate remains high despite continuous efforts to improve care for these patients (5). Oxygen and intravenous diuretics are the mainstay of treatment for AHF. Treatment aims to reduce pulmonary and peripheral congestion. Intravenous vasodilators or inotropic agents may also be required to maintain hemodynamic stability.

Management of HeFNEF is unclear. At present, no specific therapy has demonstrated mortality benefit (5). Medications such as ACEi or ARB, which are life-saving in patients with HeFREF, have not been shown to have the same effect in those with HeFNEF (14, 15).

1.3 Heart failure in the elderly

HF is a common disease in the elderly. Its prevalence continues to increase as more people survive into old age (11, 13). HF is the leading cause of hospital admissions in older adults >65 years, contributing to >5% of all medical and geriatric admissions. Elderly patients admitted for HF are at high risk of disability, recurrent admissions and increased mortality. The presence of multiple co-morbidities make diagnosis and management of elderly patients with HF clinically challenging.

1.3.1 Complex presentation

Elderly patients with HF have complex presentations, which challenges the use of traditional recommendations for diagnosis and management of HF. For instance, apart from the typical symptoms and signs of HF, elderly patients also frequently suffer from other medical conditions, which may interact with or modify the disease course. Both de novo diseases or acute decompensation of chronic conditions may trigger HF or in turn be triggered by HF, making diagnosis and management of these patients challenging.

Lately, HF has been increasingly considered as a 'cardio-geriatric syndrome' (16). Other geriatric syndromes such as frailty, cognitive impairment, poor mobility, falls, polypharmacy and urinary incontinence, are also important contributors to poor prognosis in elderly patients with HF (17, 18).

1.3.2 Difficult management

Management of HF in the elderly population is challenging. It is associated with poor outcome and high economic burden (19). The reasons are several fold:

Firstly, elderly patients with HF often suffer a clinically challenging disease course due to co-existence of complex co-morbidities, putting them at risk of both cardiac and non-cardiac complications (20).

Secondly, elderly patients are under-represented in HF trials (21). A systematic review involving 59 HF randomised controlled trials (RCT) found that the mean age of patients in HF trials was 61 years (22), which was substantially lower than that of HF patients within the general population (> 75 years) (23). Only 5% of HF trials included patients with a mean age of >75 years (22). Elderly patients are often excluded. This poses selection bias and questions the applicability of such evidence on management of the general HF population.

Thirdly, elderly patients respond differently to treatment compared to the general population. The treatment strategies we adopt in younger patients might not be effective in older patients. For example, HF therapy guided by natriuretic peptide has been shown to improve outcomes in patients aged 60 to 75 years but not in those >75 years (24). Similarly, telemonitoring in elderly patients with HF has been shown to have no significant impact on mortality or rehospitalisation rates (25).

1.4 Conclusion

Elderly patients constitute a large proportion of people living with HF. These patients are phenotypically different from younger adults with HF due to a higher co-morbidity burden and deterioration in physiological reserve. Most clinical trials in HF do not include elderly patients. Therefore, management of this cohort remains challenging. The next chapter studies the role of frailty in HF, which is central to prognosis in the elderly.

Chapter 2 Frailty and Heart Failure

2.1 Introduction

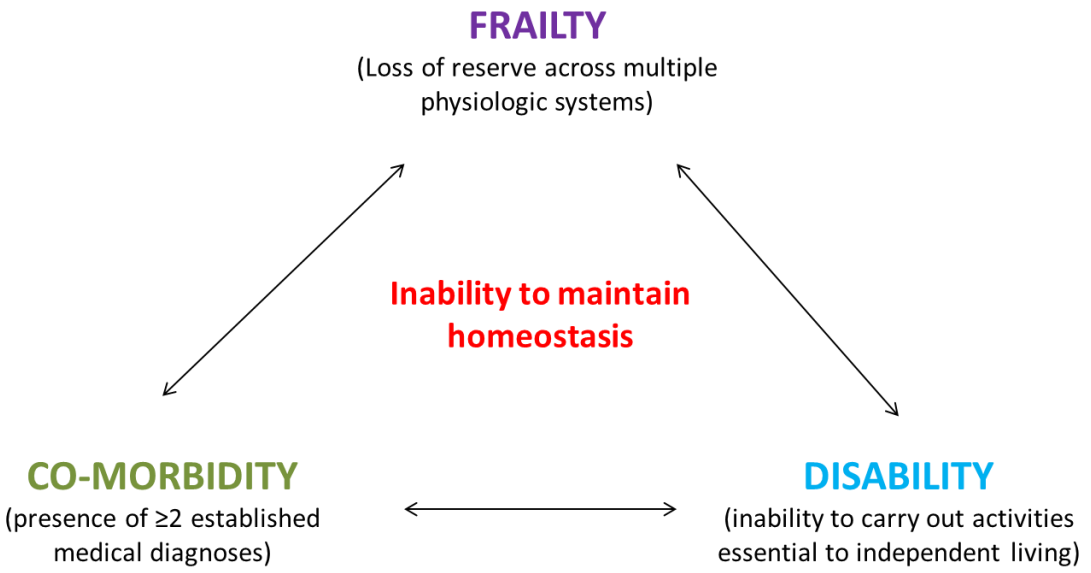
In the era of an ageing population, frailty has become an increasingly popular condition to study (26). Frailty is associated with increased morbidity and mortality (27, 28). Accurate and early identification of frailty is important, as it not only improves clinical outcome and QoL of patients but also reduces the cost of care (29).

2.2 Definition of frailty

Frailty, *frêle* in French, means "little resistance". According to a consensus group in 2013, frailty is defined as 'a medical syndrome with multiple causes and contributors that is characterised by diminished strength, endurance and reduced physiological function that increases an individual's vulnerability for developing increased dependency and/or death'(30). Frailty is a dynamic condition, which can improve and worsen over time depending on physical and/or psychological factors. Early stages of frailty can be clinically silent. However, as the reduction in reserve reaches a threshold that predisposes to serious vulnerability (usually at times of stress), the syndrome may become apparent with evident clinical, functional, behavioural and biological changes (31).

Frailty, co-morbidity and disability frequently co-occur. Although they are distinct entities, the three conditions share overlapping features and often contribute to the development or progression of each other (32). Figure 2.1 demonstrates the relation amongst the three conditions. Frailty is the subclinical/clinical loss of reserve across multiple physiological systems (33). Co-morbidity is the concurrent presence of ≥2 established medical diagnoses in the same individual. Disability is the inability to carry out activities essential to independent living (34). Abnormalities in homeostatic mechanisms due to factors such as inflammation or sympathetic-parasympathetic imbalance; might be a common pathophysiological pathway that contribute to the development of all 3 conditions (32).

Figure 2.1: Relationship amongst frailty, co-morbidity and disability



2.3 Prevalence of frailty

A systematic review including 21 community-based studies on frailty in people ≥65 years, reported that the prevalence of frailty ranged between 4% and 59% (35). Specifically, in studies which defined frailty according to the physical phenotype, the prevalence was 4-17%; whereas in studies which used other broader definitions, the prevalence was highly variable (4-59%) (35). The prevalence of frailty increased with age: 16% in patients aged 80-84 years compared to 26% in those ≥85 years (35). The prevalence of frailty in women was doubled that of men (10% vs 5%) (35).

Frailty contributes to the development and progression of cardiovascular diseases and vice versa. Frailty has been shown to be an independent predictor of HF in older adults (36). The prevalence of HF has been reported to be 6 to 8 times higher in patients who are frail compared to those who are not (37-39). On the other hand, a systematic review including 9 studies on frailty in over 54000 community dwelling older people showed that cardiovascular disease was associated with a 3-fold increased risk in developing frailty (40). Frailty is common in patients with HF, with a prevalence of 15-74% (40-43).

2.4 Frailty and outcome

There is a strong association between frailty and adverse outcomes. Frailty increases the risk of co-morbidities, falls, fractures, dependency, disability, institutionalisation, hospitalisation and mortality (27, 28, 31, 38, 39, 44). Elderly patients with cardiovascular diseases who are frail have a 2-4 fold increased risk of mortality compared those who are not frail (40). In patients with HF, frailty has been shown to predict worse QoL, increased frequency of HF decompensation, rehospitalisations and mortality (19, 40, 42).

2.5 Pathophysiology

2.5.1 Ageing and frailty

Ageing is the decline in functional properties at the cellular, tissue and organ level, which predisposes to homeostatic failure (45). Frailty is a consequence of pathological ageing, characterised by multi-system dysregulation, leading to reduced homeostatic capacity and increased vulnerability to stressors (44, 46).

Ageing and frailty are associated with abnormal cellular responses to stressors. Apoptosis is an orderly process of cellular self-destruction, which is essential for remodelling of tissues and maintenance of organ function (47). Ageing dysregulates apoptosis and promotes necrotic cell death (48). Accelerated apoptosis of skeletal muscle has been implicated in pathogenesis of sarcopenia and frailty (49). Ageing is also associated with accumulation of senescent cells, which exhibit abnormal cellular function (50, 51). Furthermore, ageing disrupts cellular repair mechanisms, compromising the functional capacity of organelles (52). These cellular changes drive chronic inflammation.

Ageing and frailty are also associated with abnormal systemic responses to stressors. Inflammation is a key systemic response to stressors. Ageing is associated with an imbalance in inflammatory cytokines. This results in dysfunction of the adaptive and innate immunity which drives further inflammation (53). Inflammation is potentially a key pathophysiological factor, contributing directly to frailty and other associated

pathologies such as Parkinson's disease, depression and dementia (54-58). Inflammation has also been postulated to induce sickness behaviour and cause fatigue, changes in sleep pattern, impaired concentration and social functioning (59). Furthermore, inflammation disrupts the corticosteroid neuroendocrine negative feedback mechanism, causing hypothalamic-pituitary-adrenal (HPA) axis hyperactivity (60). These systemic changes in turn dysregulates cellular function.

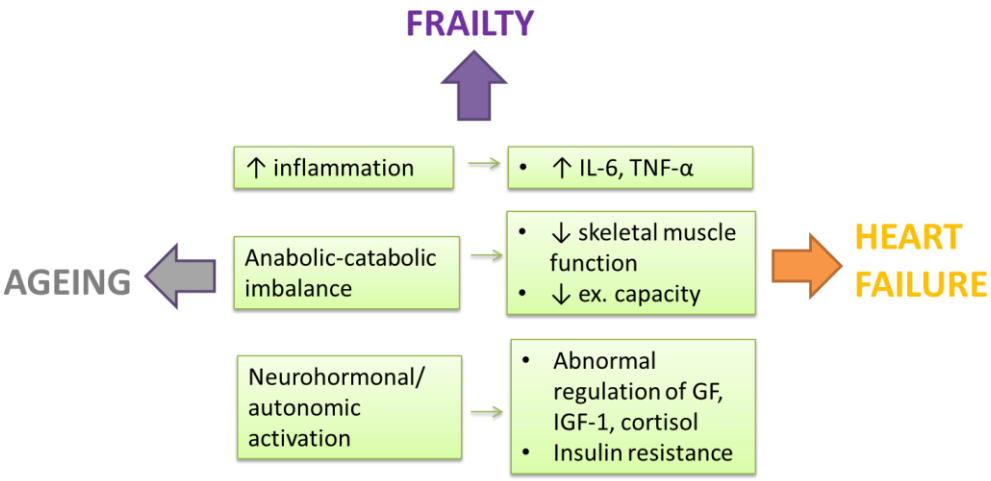
2.5.2 Frailty and heart failure

The pathophysiology of frailty in patients with HF is unknown. Due to the commonalities between the two conditions, it is likely that their pathophysiological mechanisms overlap.

HF and frailty are both inflammatory conditions, characterised by upregulation of inflammatory cytokines such as interleukin (IL)-6, C-reactive protein and tumor necrosis factor alpha (TNFα) (19, 41, 61). Both conditions arise secondary to anabolic-catabolic imbalance, resulting in decline in skeletal muscle function and exercise capacity (19). Thirdly, both conditions involve activation of the neuro-hormonal and autonomic nervous systems, resulting is insulin resistance and dysregulation of growth factors (GF), insulin-like growth factor (IGF)-1 and cortisol (19). (Figure 2.2)

It is difficult to establish a cause-effect relationship between frailty and HF. On one hand, frailty reduces myocardial resistance to stressors such as ischaemia, arrhythmias and volume overload, predisposing to myocardial injury, decompensation and hospitalisation (61). On the other hand, HF-associated breathlessness, fatigue and peripheral oedema, leads to reduced functional capacity, predisposing to frailty. HF also reduces cerebral perfusion, predisposing to falls, cognitive decline and ultimately frailty and disability (42).

Figure 2.2 Summary of common pathophysiological mechanisms amongst ageing, frailty and HF.



IL= interleukin, TNF-α = tumor necrosis factor – alpha, ex = exercise, GF = growth factor, IGF = insulin-like growth factor

2.6 Frailty, heart failure and related conditions

Frailty and HF both affect multiple systems and are associated with a wide range of medical conditions such as sarcopenia, cachexia and neuropsychiatric conditions (30, 41, 61).

2.6.1 Sarcopenia

Hippocrates described HF as a condition in which 'the flesh is consumed and becomes water…the abdomen fills with water; the feet and legs swell; the shoulders, clavicles, chest, and thighs melt away'(62).

Sarcopenia is the loss of skeletal muscle mass, power and strength (63). It is not only a well-observed feature in patients with HF; but also a key component of the frailty syndrome. In patients with HF and/or frailty: physical inactivity, malnutrition, chronic inflammation, hypercatabolism and abnormal activation of the neuroendocrine and sympathetic systems, have been postulated to disrupt the delicate balance of muscle homeostasis, leading to muscle breakdown and loss of strength, causing further reduction in functional capacity (63, 64).

2.6.2 Cachexia

The term ‘cachexia’ originates from the Greek words *‘kakos’* and *‘hexis’*, meaning “bad condition”. Cardiac cachexia represents end-stage body wasting in patients with advanced HF (65). Cachexia is a complex metabolic syndrome characterised by weight loss of ≥5% in 12 months in addition to satisfying at least 3 of the following 5 criteria: decreased muscle strength; fatigue; anorexia; low fat mass index and abnormal biochemistry (inflammation, anaemia or low serum sodium) (66). Cachexia involves wasting of all body components including muscle and fat mass as well as bone density. It is different from sarcopenia, which is characterised by isolated loss of muscle mass.

Although frailty and cachexia share common features such as muscle weakness and fatigue, they are distinct entities. Frailty is the progressive decline is physiological reserve associated with ageing and usually occurs in older patients, whereas cachexia is associated with chronic diseases and can occur in younger patients. Whilst weight loss is essential for diagnosing cachexia, it does not have to be present in order for a patient to be classified as frail. In frail patients who are sarcopenic, the loss in muscle mass is often counterbalanced by an increase in total body fat, a phenomenon known as ‘sarcopenic obesity’ (67).

2.6.3 Cognitive impairment

Cognitive impairment is a common co-morbidity in elderly patients with HF, with an incidence ranging between 25% and 80% (68). Apart from physical deconditioning, cognitive decline has also been increasingly recognised as a contributing factor for development of frailty (31). On one hand, age-related brain pathologies including Alzheimer’s disease, neuronal loss in the substantia nigra and macro or micro-infarcts have been shown to be independent predictors of physical frailty (69). On the other hand, physical frailty has also been shown to be associated with a faster rate of cognitive decline (70). Concomitant presence of frailty and delirium in elderly patients admitted to hospital is associated with a particularly poor outcome (71).

2.7 Frailty models

Accurate identification of frailty in patients with HF is important; not only to improve clinical outcome and QoL of patients, but also to reduce the cost of care (29). In general, there are two basic concepts of frailty: Fried frailty phenotype (44) and the Deficit index (72).

2.7.1 Fried frailty phenotype

Fried frailty phenotype was proposed by Fried and colleagues in 2001, based on a secondary analysis of the Cardiovascular Health Study (44). The group defined frailty as a physical syndrome using five criteria: unintentional weight loss, self-reported exhaustion, slow walking speed, weakness and reduced physical activity. An individual is classified as 'frail' if 3 or more of the above criteria were met.

Fried frailty criteria is one of the most commonly used frailty tools in the literature. It is precise, clear and easy to measure. The criteria has a strong correlation with physiological alterations such as activation of the inflammation and coagulation systems (73).

Fried criteria has been extensively validated to predict adverse health outcomes (74). However, this frailty concept is not without flaws. Firstly, Fried criteria lacks sensitivity and specificity in detecting frailty, especially when used in patients with Parkinson's disease, dementia and some malignancies (75). Secondly, Fried criteria does not grade the severity of frailty. This can be problematic as there is marked heterogeneity in the risk of adverse outcomes in people who are deemed 'frail'. Thirdly, there is ongoing controversy regarding the nature and number of items included in Fried criteria (76). Fried criteria focuses on physical frailty and does not take into account other contributing factors such as psychological affect, cognition and other co-morbidities. Some may also argue that certain components of the criteria can be deducted, as they are likely to be highly correlated with each other.

2.7.2 Deficit index

The deficit index was developed by Mitnitski and colleagues in 2001 as part of the Canadian Study of Health and Ageing (72). The group defined frailty as a state of vulnerability due to accumulation of health deficits (72). They created a deficit index (DI) to quantify frailty using 92 baseline variables including symptoms, signs, disability and laboratory tests. The DI was calculated as the ratio of health deficits present in an individual against the total number of variables assessed. A higher DI compared to a lower DI, irrespective of age, was associated with increased risk of mortality and institutionalisation (75).

The DI has many advantages. Firstly, there is no limitation as to which health deficits should be included as long as the following criteria are met: there are at least 30 health deficits; each deficit has a prevalence of at least 1% in the population studied and is associated with worse outcomes (77, 78). This creates a degree of flexibility for frailty evaluation. The DI is also a robust tool which takes into account multiple dimensions of frailty. It has been widely studied using different combinations of health deficits and proven to have significant prognostic value (76). However, the DI also has its limitations. It requires a vast amount of health information and is time-consuming to perform. Therefore, application of the DI may not be feasible in certain clinical settings.

2.8 Frailty tools

Many tools have been proposed to measure frailty. Most were derived from the Fried criteria and the DI. Frailty tools developed from the Fried criteria focus on assessing physical frailty. Examples include the short physical performance battery (SPPB) (79). Frailty tools developed from the DI focus on multi-dimensional assessment of frailty. Examples include the Edmonton frailty scale (EFS) (80), Groningen frailty index (81) and Tilburg frailty indicator (82).

The comprehensive geriatric assessment (CGA) offers the most holistic approach to frailty evaluation. It assesses multiple domains including cognitive decline, emotional instability, social status and physical function (83). However, the CGA is time-consuming to perform and inappropriate for use in busy clinical settings.

Recently, novel frailty screening tools, which are quick and easy to use, have been proposed. Examples include the clinical frailty scale (CFS) (84), Derby frailty index (DFI) (85) and the Acute Frailty Network (AFN) frailty criteria (86, 87). The CFS is a 9-point judgement-based screening tool, which takes into account cognition, mobility, function and co-morbidities. It is simple to use and has been shown to predict mortality and institutionalisation in elderly patients (84).

Single physical tests have been introduced to increase the objectivity of frailty evaluation. Examples include walk tests, gait speed and grip strength. Boxer and colleagues found moderate agreement between the 6-minute walk test and Fried criteria as a measure of frailty in patients with HeFREF (88). A slow gait speed of <1 metre per second has been shown to identify individuals at increased risk of death (89). Furthermore, a meta-analysis involving over 23,000 patients with cardiac disorders showed that reduced grip strength predicted death and HF hospitalisation (90).

2.9 Conclusion

Frailty is common in patients with HF and is associated with poor outcomes. Pathogenesis of frailty in HF is complex. The two basic concepts of frailty - Fried criteria and DI, have led to the development of numerous frailty tools. However, there is no consensus as to which tool is best to use in patients with HF.

Chapter 3 Malnutrition and Heart Failure

3.1 Introduction

Similar to frailty, malnutrition is common in patients with HF. It is not only associated with functional decline and poor QoL; it also predisposes to morbidity and mortality; all of which increases healthcare costs (91).

Malnutrition often goes undiagnosed, especially in patients who have high body mass index (BMI). Patients with HF are at risk of developing malnutrition due to several reasons. Firstly, HF is a catabolic syndrome associated with increased resting energy expenditure. Secondly, HF also causes congestive enteropathy, leading to malabsorption and gastrointestinal symptoms such as anorexia and nausea (92). These factors predispose to weight loss, sarcopenia and ultimately cachexia.

In this chapter, I will explore the role of malnutrition in patients with HF, focusing on its prevalence, pathophysiology and prognostic significance.

3.2 Definition of malnutrition

There is currently no clear agreement on the definition for malnutrition. According to the Academy of Nutrition and Dietetics and the American Society for Parenteral and Enteral Nutrition (ASPEN), a patient is malnourished if he/she fulfils 2 of the following criteria: inefficient energy intake; weight loss; loss of muscle mass or subcutaneous fat; localised or generalised fluid accumulation and diminished functional status measured by hand grip strength (93).

3.3 Prevalence of malnutrition

Malnutrition is common in patients with HF. Its prevalence varies according to the definition of malnutrition and the population studied. According to the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca-Heart Failure

(GISSI-HF) trial and the Valsartan Heart Failure Trial (Val-HeFT), 16% of patients with HF had significant weight loss of >5%; this was higher at 42% according to the Studies of Left Ventricular Dysfunction (SOLVD) trial (94, 95). The prevalence of malnutrition in patients hospitalised with HF has been reported to range between 30-70% (96, 97).

3.4 Malnutrition, weight loss and outcome

Malnutrition is related to recurrent hospitalisations, longer length of stay and mortality (91). An Australian study examining >3000 patients admitted to hospital, found that malnourished patients compared to well-nourished patients, had a 5 day longer median length of stay and 8% higher 90-day readmission rate (98). Weight loss of >5% has been shown in the GISSI-HF and Val-HeFT study to be an independent predictor of mortality (94). According to the Candesartan in Heart Failure – assessment of reduction in mortality and morbidity (CHARM) study, patients with HF with weight loss of >5% over 6 months, had >50% increased risk of cardiovascular and non-cardiovascular mortality compared to patients with stable weight (99). A post-hoc analysis of the SOLVD trial concluded that weight loss of >6% was associated with a 2-fold increased risk of mortality (95).

Interestingly, some studies have suggested that weight loss might not be associated with an adverse prognosis in some patients with HF. Trullas and colleagues analysed weight change in >700 patients with HF from the Spanish National Heart Failure Registry (Registro Nacional de Insuficencia Cardiaca (RICA)) (100). They found that 21% of patients experienced weight loss of >5%. However, this was not associated with increased mortality or readmission (100). In fact, in obese patients with HF, intentional weight loss of up to 5% (achieved through dietary programmes) has been shown to improve symptom control, functional ability, QoL and cardiac function in terms of LVEF, although there were no mortality data reported (101).

The relation between baseline BMI and weight loss on mortality in patients with HF is unclear. The SOLVD trial showed that any weight loss independent of the patient's baseline weight is associated with poor survival (95). The CHARM study, however,

suggested that weight loss in patients who were lean at baseline, had a particularly high risk of mortality (99). Another study which assessed 1000 consecutive ambulatory patients with HF, reported that an annual weight loss of >5% was associated with a high risk of mortality, more so in the obese compared to non-obese patients (102).

3.5 Obesity paradox

The prevalence of obesity in patients with HF reaches almost 50% (103). Obesity in the general population is associated with adverse outcomes such as the development of HF and cardiovascular death. However, obesity in patients with established HF, has been shown to be associated with significant survival benefit (104). This phenomenon is known as the "obesity paradox" (105).

Fonarow and colleagues analysed >80,000 patients with HF from the Acute Decompensated HF National Registry in America. They found that for every 5 unit increase in BMI, there was a 10% lower mortality risk (106). Patients with HF who are obese may have more metabolic reserve to tolerate the catabolic stress of HF compared to non-obese patients. However, this was not a universal observation (107). A study involving 7788 patients with CHF in the Digitalis Investigation Group trial, showed that obesity (BMI $\geq$30 kg/m^2) did not confer survival benefit (107) .

3.6 Pathophysiology

3.6.1 Inadequate nutritional intake

Patients with HF often suffer inadequate nutritional intake due to several reasons. Firstly, HF is associated with breathlessness, fatigue and peripheral oedema, which leads to poor exercise tolerance and mobility. Poor symptom control impacts on patients' ability to self-care and prepare meals (108). Secondly, bowel congestion and ascites, lead to gut hypomobility, constipation and anorexia (92). Thirdly, side effects

of HF medications might also cause dysgeusia and anorexia (109). Inadequate protein and calorie intake results in weight loss and cachexia.

3.6.2 Hypercatabolism

HF is a hyper-catabolic syndrome. It is associated with increased work of breathing and chronic inflammation, which results in higher resting energy expenditure (110). Chronic inflammation not only reduces anabolism, it also causes insulin resistance and promotes catabolism of skeletal muscles, fat and eventually bone tissues, resulting in body wasting (111, 112).

3.6.3 Nutritional deficiencies

Patients with HF often suffer nutritional deficiencies as a result of poor oral intake (113). Taurine is an amino acid which is essential in cardiac metabolism (113). Taurine supplementation has been shown to improve exercise capacity in patients with HF (114). L-carnitine is an amino acid derivative that modulates energy metabolism (115). L-carnitine supplementation has been shown to improve cardiac function and symptoms in patients with HF (115).

Coenzyme Q10 (CoQ10) is a coenzyme for mitochondrial enzymes and a cell membrane stabiliser (116). CoQ10 supplementation has been shown to improve LVEF and hard outcomes in patients with HF with minimal side effects (116).

Omega-3 polyunsaturated fatty acids (PUFA) might have a role to play in preserving cardiac mitochondrial function and inhibiting production of inflammatory cytokines (117). A recent meta-analysis showed that omega-3 PUFA supplementation led to lower natriuretic peptide levels but did not improve LVEF or exercise capacity (117).

Deficiencies in selenium, magnesium, potassium, zinc and vitamin D are also common in patients with HF and might disrupt energy metabolism of the myocardium (113). Further studies are needed to clarify the role of correcting such deficiencies in patients with HF.

3.7 Identification of malnutrition

Many tools have been proposed to identify malnutrition. However, there is no standard of method of evaluating malnutrition in patients with HF (118).

3.7.1 Anthropometric measurements

Anthropometric measurements are used to estimate body composition. Methods commonly used in clinical practice include measurement of weight, height, skinfold thickness and bioelectrical impedance analysis. Lower BMI, smaller waist circumference and lower fat mass on bioelectrical impedance analysis, have been shown to be independent predictors of mortality in HF patients (119, 120). However, weight and BMI might not be an accurate reflection of nutritional status in patients with HF. They do not discriminate between lean and fat mass; and are influenced by fluctuation in volume status, which is likely to be related to the disease itself or secondary to medical therapies rather than poor nutrition (121).

3.7.2 Biochemical tests

Serum albumin has been shown to be a marker of poor nutritional status and is associated with increased morbidity and mortality (122). Disadvantages to using albumin in isolation as a diagnostic tool for malnutrition include the fact that albumin levels fluctuate as a result of acute illness, inflammation, liver dysfunction and/or haemodilution. Secondly, albumin also has a large body pool and a long half-life (~20 days). Therefore it might not reflect acute changes in nutritional status (123).

Malnutrition has also been shown to be associated with alterations in immune function (124). However, individual immune markers, such as total lymphocyte count, have a limited role in nutritional assessment as they lack sensitivity and specificity (125).

The role of high sensitivity C-reactive protein (hsCRP) in evaluating malnutrition is unclear. Some studies demonstrate an independent association between increasing hsCRP and significant weight loss (94), however, other studies reported no such association (102).

Other biomarkers such as pre-albumin, transferrin and insulin-like growth factor-1, have been proposed to predict nutritional status, but they lack sensitivity and specificity and are not commonly used (126-128).

3.7.3 Cardiac function

Severe tricuspid regurgitation and increased right atrial pressure were found to be predictors of malnutrition but not LVEF or left-sided cardiac pressures (129).

3.7.4 Physical tests

Hand grip strength predicts morbidity and mortality (90). It has been shown to be a better predictor of post-operative morbidity in surgical patients compared to other nutritional markers such as arm circumference, weight loss and albumin levels (130).

3.7.5 Simple malnutrition scores

In order to improve diagnostic accuracy, individual laboratory tests and anthropometric measures have been combined to form malnutrition scores. These scores are simple, easy to use and have been shown to predict mortality (118). Examples of simple malnutrition scores include: controlling nutritional status (CONUT) score, prognostic nutritional index (PNI), geriatric nutritional risk index (GNRI), nutritional risk index and instant nutritional assessment (131-135). Further details about some of these scores can be found in Chapter 4.

3.7.6 Multi-dimensional tools

Multi-dimensional tools offer a more comprehensive assessment of nutritional status than simple malnutrition scores. Multi-dimensional tools take into account laboratory data, dietary intake, co-morbidities, functional status, anthropometric measures and physical examination findings. Examples of multi-dimensional tools include the malnutrition universal screening tool (MUST), mini nutritional assessment (MNA) and subjective global assessment (SGA) (136-138). Further details about these tools can be found in Chapter 4.

3.8 Conclusion

There is currently no universal definition or diagnostic criteria for malnutrition, although many tools for its evaluation have been proposed. Malnutrition is common in patients with HF and is associated with a poor prognosis. However, there is no consensus on how to best evaluate malnutrition in patients with HF.

Chapter 4 Methodology

4.1 Rationale behind my thesis

The National Heart Failure Audit was established in 2007 (4). It aimed to capture data on the clinical management of patients with HF, highlight clinical practice which do not meet standards and facilitate service improvement (4). I participated in data collection for the National HF Audit in 2013 at the Diana, Princess of Wales Hospital, Grimsby.

During the audit, I made several interesting observations regarding the management of patients admitted with HF. Firstly, in contrary to the normal expectation that patients admitted with HF would be managed in a cardiology ward, I found that around 50% of patients were managed in a general medical or geriatric ward. The place of care is important as it directly impacts on patient outcome. According to the National HF Audit, patients managed in a cardiology ward, compared to those managed in other medical wards, had a lower in-patient mortality (6% vs 10%) (4).

Secondly, I found that most patients admitted for HF were elderly. They often suffer prolonged hospitalisations and have high mortality rates. According to the National HF Audit, the median age of patients admitted with HF was 81 years (4). Patients ≥75 years have a much higher in-hospital mortality rate compared to those <75 years (11% vs 4%) (4).

Thirdly, frailty and malnutrition appeared to be common in elderly patients admitted with HF and were associated with poor outcome. However, they were often neglected. Understanding frailty and malnutrition is vital to inform the design of future intervention trials to improve outcomes in elderly patients with HF. In Chapters 2 and 3, I have demonstrated a gap in our knowledge regarding the definition and identification of frailty and malnutrition in patients with HF. In the following chapters, I will attempt to find an answer to these questions by studying the prevalence and prognostic role of frailty and malnutrition in different cohorts of patients with HF.

4.2 Aims

The primary aim of this thesis is to study the prevalence, clinical associations and prognostic role of frailty and malnutrition in different populations of patients with HF. The secondary aim is to investigate possible pathophysiological mechanisms underlying malnutrition and frailty in patients with HF. To achieve the above aims, I have conducted several studies. The aims of individual studies are listed below:

In chapter 5, I aimed to study the prevalence, clinical associations and prognostic role of frailty and malnutrition in patients admitted acutely to hospital with HF, using 3 frailty screening tools and 3 simple malnutrition tools.

In chapter 6, I aimed to study the prevalence, clinical associations and prognostic role of malnutrition in patients with CHF, using 3 simple malnutrition tools.

In chapters 7 and 8, I aimed to compare the agreement, classification performance and prognostic role amongst 9 commonly used frailty tools (3 screening tools, 3 assessment tools and 3 physical tests) in patients with CHF.

In chapters 9 and 10, I aimed to compare the agreement, classification performance and prognostic role amongst 9 commonly used malnutrition tools (3 simple tools, 3 multi-dimensional tools and 3 laboratory tests) in patients with CHF.

In chapter 11, I aimed to study the relation between malnutrition and congestion and the association between these two features and mortality in patients with CHF.

In chapter 12, I aimed to study the effects of sympathetic blockade on weight change and mortality in patients with CHF.

4.3 Methods of investigation

This section outlines the general design and execution of the 6 primary studies included in this thesis. Additional information regarding end points and statistical analyses specific for each study will be discussed in individual chapters separately.

4.3.1 Study populations

Chapter 5: This study was carried out at the Diana Princess of Wales Hospital, Grimsby, which is a district general hospital within the Northern Lincolnshire and Goole Hospitals NHS Foundation Trust, UK. The hospital has approximately 200 HF admissions per year. Over a 24 month period between January 2013 and December 2014, I prospectively recruited 265 consecutive patients admitted with a primary diagnosis of HF secondary to left ventricular systolic dysfunction (LVSD).

Chapters 6-12: These studies were carried out at our community HF clinic, based at the Castle Hill Hospital, Hull, UK. Our clinic serves a local population of about 500,000 people. From 2000, patients referred by either primary or secondary care physicians to our HF clinic were enrolled in a longitudinal observational study of patients with CHF (The Hull LifeLab). Some patients had no prior diagnosis of CHF and were treatment naive, therefore requiring initiation of guideline-recommended therapy; others had a pre-existing diagnosis of CHF and had already been initiated on treatment that might, however, require optimisation. Inclusion and exclusion criteria of individual studies are listed below:

Chapter 6: I retrospectively enrolled consecutive patients from the Hull Lifelab between 2000 and 2016 who had measurements of height, weight and N-terminal pro-B-type natriuretic peptide (NT-proBNP) at baseline visit.

Chapter 7 to 10: I prospectively enrolled consecutive patients from the Hull Lifelab, who attended follow up at our clinic between September 2016 and March 2017. I included patients who had a pre-existing (> 1 year) clinical diagnosis of CHF; who had already been initiated on guideline indicated anti-HF treatments and were regularly followed up at our department.

I also invited individuals who had consented to take part in research at our department as control subjects to participate in this study. Individuals who fulfilled the following criteria were recruited as control subjects for Chapter 7 and 9: 1) >65 years; 2) no previous or current symptoms or signs of HF; 3) normal left ventricular (LV) systolic function on echocardiography; 4) risk factors for developing HF, including coronary artery disease, diabetes mellitus or HTN.

Chapter 11: I retrospectively enrolled a subset of patients from the Hull Lifelab between 2008 and 2012 who had had a detailed echocardiographic examination at baseline visit.

Chapter 12: I retrospectively enrolled consecutive patients from Hull Lifelab between 2000 and 2016 who had weight measurements recorded both at baseline and at 1 year follow up.

4.3.2 Definition and classification of heart failure

HF is defined as the presence of symptoms or signs of HF and evidence of cardiac dysfunction; either a LVEF <40% **or** a raised plasma concentration of NT-proBNP.

In Chapter 5, I defined LVSD as LVEF <40% or at least moderate LVSD by visual inspection on echocardiography if LVEF was not available.

In Chapters 6 to 12, I classified patients with HF into those with reduced ejection fraction (HeFREF) and normal ejection fraction (HeFNEF) as follows:

- HeFREF: LVEF <40% (or at least moderate LVSD by visual inspection on echocardiography if LVEF was not available)
- HeFNEF: LVEF ≥40% (or better than, or equal to, mild-moderate LVSD by visual inspection on echocardiography if LVEF was not available) and raised plasma concentrations of NT-proBNP.

In Chapters 6, 12 and 13, I defined raised NT-proBNP as levels >125ng/L according to the ESC guidelines (5). In Chapters 7 to 10, I defined raised NT-proBNP as levels >400ng/L according to the National Institute of Clinical Excellence (NICE) guidelines (10). I used the NT-proBNP cutoff from the latest guideline available on the management of HF at the time of data analysis.

Patients with an LVEF ≥40% and NT-proBNP ≤125ng/L were not regarded to have HF.

4.3.3 Co-morbidities

I measured co-morbidities using the Charlson co-morbidity score (139). (Table 4.1) Table 4.2 detailed the definitions of medical conditions included in the Charlson co-morbidity score.

Table 4.1: Charlson co-morbidity score (*For each decade >40 years, a score of 1 is added to the total score)

Score*	Condition
1	Myocardial infarction Congestive heart failure Peripheral vascular disease Cerebrovascular disease: Stroke with mild/ no residua; transient ischaemic attack (TIA) Dementia Chronic pulmonary disease Connective tissue disease Peptic ulcer disease Mild liver disease Diabetes without endo organ damage (excludes diet-controlled alone)
2	Hemiplegia Moderate/ severe renal disease Diabetes with end-organ damage Tumor without metastases (exclude if > 5 years from diagnosis) Leukaemia Lymphoma
3	Moderate/ severe liver disease
6	Metastatic solid tumor Acquired immune deficiency syndrome (AIDS)

Table 4.2: Definition of medical conditions.

Condition	Definition
Ischaemic heart disease	Previous medical history of acute coronary syndrome (ACS), percutaneous coronary intervention or coronary artery bypass surgery, or diagnosis of myocardial ischemia based on invasive or non-invasive diagnostic tests.
Myocardial infarction	An episode of acute chest pain or an equivalent clinical event requiring hospitalisation with ischaemic electrocardiographic and/or enzyme changes.
Hypertension	Systolic blood pressure (BP) ≥140 mmHg, diastolic BP ≥90 mmHg (140) or a previous clinical diagnosis.
Hyperlipidaemia	Pre-existing hypercholesterolemia/ hypertriglyceridemia requiring treatment with statins or fibrates.
Cerebrovascular disease (CVD)	Any previous history of stroke or TIA.
Hemiplegia	Paralysis of one entire side of the body either as a result of cerebrovascular accident or other conditions.
Peripheral vascular disease (PVD)	Evidence of extra-cardiac arterial disease at ultrasound, such as those of the lower limbs and abdominal aorta.
Chronic pulmonary disease	Asthma, chronic obstructive pulmonary disease and other chronic lung diseases which cause ongoing symptoms such as dyspnoea or cough with mild or moderate activity.
Anaemia	Serum haemoglobin (Hb) level <12g/dL for females and <13g/dL for males (141).
Diabetes Mellitus	Symptoms (e.g. polyuria, polydipsia and unexplained weight loss) plus random or fasting venous plasma glucose concentration ≥11.1 and ≥7.0 mmol/l respectively (142). End-organ damage include retinopathy, neuropathy and nephropathy.
Depression	Pre-existing diagnosis of depression requiring treatment with anti-depressives.
Renal disease	Mild: estimated glomerular filtration rate (eGFR) 60-89 (ml/min/1.73m^2) Moderate: eGFR 30-59 Severe: eGFR<30 (143).
Liver disease	Mild: without portal hypertension Moderate: with portal hypertension but without bleeding Severe: with portal hypertension and variceal bleeding or requiring transplantation (139).
Peptic ulcer disease	Ulcers in the stomach or duodenum which have required treatment

Table 4.2 (continued): Definition of medical conditions.

Condition	Definition
Dementia	Moderate to severe chronic cognitive deficit resulting in impaired function from any cause.
Rheumatologic/ connective tissue disease	History of systemic lupus erythematosus, polymyositis, mixed connective tissue disease, rheumatoid arthritis, polymyalgia, vasculitis, sarcoidosis, Sjogrens syndrome or other systemic vasculitis
Lymphoma	History of Hodgkin's or non-Hodgkin's lymphoma.
Leukaemia	History of acute or chronic myelogenous or lymphocytic leukaemia.
Solid tumor	Primary tumor of solid organs including breast, colon, lung or prostate.
AIDS	Final stage of human immunodeficiency virus (HIV) infection where opportunistic infections or HIV-related cancers occur as a result of a weakened immune system.

4.3.4 Routine examination

All subjects had a routine examination during each clinic visit, which includes a full medical history, a physical examination, blood tests, an ECG, an echocardiogram and a consultation with a HF specialist.

A medical history includes exploration and quantification of HF symptoms such as breathlessness, fatigue and peripheral oedema; review of general health, co-morbidities and medications.

A physical examination includes a record of heart rate, blood pressure, height and weight measurement. In Chapter 5, weight was measured on the first day of admission, with subjects in a hospital gown and without their shoes. In Chapters 6 to 12, weight was measured at our community HF clinic with subjects in their casual wear without shoes. BMI was calculated using the formula: BMI = weight in kilograms/ (height in meters) squared. Blood tests were performed for standard haematology and biochemistry profiles (including full blood count, electrolyte levels, renal and liver function tests) and NT-proBNP.

An ECG was performed by an experienced nurse and interpreted by a HF specialist. Cardiac rhythm was classified as follows: sinus rhythm (SR) or atrial flutter/fibrillation (AF); paced or non-paced rhythm.

An echocardiogram was performed by an experienced sonographer using a Vivid 5, 7 or 9 Scanner (GE, Fairfield, Connecticut, USA). In Chapter 5, all subjects had an echocardiogram performed within the first 24 hours of admission. In Chapters 6 to 12, all subjects had an echocardiogram as part of their assessment at our HF clinic. LVEF was calculated using Simpson's method. If LVEF could not be calculated, LV systolic impairment was visually estimated as none; or trivial, mild, mild-moderate, moderate, moderate-severe or severe.

4.3.5 Frailty evaluation

Frailty screening tools

In Chapters 5,7 and 8, I screened subjects for frailty using the following 3 screening tools. For each subject, I reviewed the medical and nursing notes together with assessments performed by the multidisciplinary healthcare team including physiotherapists, occupational therapists, dieticians and pharmacists.

1) *The Derby frailty index (DFI; scores as frail vs non-frail)*
   DFI is a quick pragmatic frailty identification tool initially developed in 2013 (85). A subject is classified as frail if one of the following criteria was met: 1) ≥65 years and a care home resident; 2) ≥75 years with confusion, falls or reduced mobility; 3) ≥85years with >4 co-morbidities (85).

2) *The Acute Frailty Network criteria (AFN; scores as frail vs non-frail)*
   AFN defines frailty as present in (a) people aged ≥85 years or (b) people aged ≥65 with one or more of the following presenting features: cognitive impairment;

resident in a care home; history of fragility fractures; Parkinson's disease; recurrent falls (86, 87).

3) *Clinical frailty scale (CFS; measures between 1 (very fit) and 9 (terminally ill))*
Subjects are scored according to their functional capacity, level of dependence co-morbidities. For example, an individual with uncontrolled symptoms who is not frankly dependent is classified as vulnerable and scores 4 on the CFS; while an individual with limited dependence on others for instrumental activities of daily living including finances, transportation, heavy housework and medications will be classified as mildly frail and scores 5 on the CFS (Figure 4.1). Subjects with CFS 1-3, 4, 5, 6 and 7-9 are classified as non-frail, pre-frail, mildly, moderately and severely frail respectively. Subjects with a CFS >4 are classified as frail (74, 84).

Figure 4.1 Clinical frailty scale

Frailty assessment tools

In chapters 7 and 8, I performed longer assessments for frailty using the following 3 assessment tools. Frailty assessments consider a variety of factors e.g. weight loss, cognition, mood, co-morbidities and functional performance.

1) *Fried frailty phenotype* (measures between 0 (normal) and 5 (very frail)):
   The Fried frailty phenotype considers frailty as a clinical syndrome using five criteria: 1) unintentional weight loss (>10 lbs [>4.5 kg] in the past year); 2) self-reported exhaustion; 3) weakness (low grip strength); 4) slow walking speed (time to walk 5 meters ≥6-7 seconds depending on sex and height); and 5) low physical activity (low weekly total energy expenditure) (44). To evaluate weekly total energy expenditure, I used the Minnesota leisure time activity questionnaire (144). Each physical activity was assigned a unique intensity code, described as the metabolic equivalent (MET) value (145). Total energy expenditure (Kcal/week) = time spent on each physical activity (in minutes) x corresponding MET of the activity. A detailed description of individual components of the Fried criteria can be found in Figure 4.2. A point was given for each criterion met. Subjects with ≥3 points were classified as frail and those with 1-2 points and 0 points were classified as pre-frail and non-frail respectively (44).

2) Edmo*nton frailty scale* (EFS; measures between 0-17)
   EFS is a multi-dimensional frailty assessment tool which includes general health status, functional independence, social support, cognition, medication use, nutrition, continence and mood (80). EFS has been validated against the comprehensive geriatric assessment (CGA) (83), a multi-dimensional, multidisciplinary diagnostic process used to determine medical, functional and psychosocial problems in elderly patients (80). Subjects with EFS 0-5 were classified as non-frail, those with EFS 6-7, 8-9, 10-11 and 12-17 were classified as vulnerable, mildly, moderately and severely frail respectively. Subjects with EFS ≥ 8 were classified as frail (Table 4.3).

3) *The Deficit Index* (DI; measures between 0.03-0.72)

Mitnitski and Rockwood consider frailty as a clinical state as a result of accumulation of deficits (72). These deficits are combined in an index score to reflect the proportion of potential deficits present in a person. I selected 32 deficits according to previously published criteria (77) to construct the Deficit Index. The first 13 items of the DI were related to activities of daily living which were collected by direct questioning of participants. The remaining items were based on information from patient's medical records or physical tests during the visit (Table 4.4). If a subject exhibited 5 out of the 32 possible deficits, the Deficit Index for that patient would be 5/32 or 0.16.

In chapter 7, I stratified subjects according to terciles of DI; those in the lower tercile were classified as non-frail while those in the middle and upper terciles were classified as pre-frail and frail respectively.

In chapter 8, I further stratified subjects according to quintiles of DI; those in the lowest quintile were classified as non-frail; those in the subsequent quintiles were classified as pre-frail, mildly, moderately and severely frail respectively.

Figure 4.2: Fried frailty phenotype.

- **Weight loss:** Frail if weight loss >10 pounds over past year or ≥ 5% of previous year's body weight

- **Exhaustion:** Frail if answering 2 or 3 to either of these questions:
  1) How often in the last week did you feel like everything you did was an effort?
  2) How often in the last week did you feel like you cannot get going?

  Answers include:
  0 = rarely/ none of the time (≤1 day); 1 = some or a little of the time (1–2 days);
  2 = a moderate amount of the time (3–4 days); 3 = most of the time.

- **Physical Activity:** I used the Minnesota leisure time activity questionnaire to assess the time spent per week on the listed activities over the previous 3 months. Each physical activity has a corresponding metabolic equivalent (MET) value as an indicator of activity intensity. Total energy expenditure (Kcal/week) = time spent on each physical activity category (in minutes) x corresponding MET value.

	Total energy expenditure (kcal/week) criterion for frailty
Male	≤ 383
Female	≤ 270

Physical Activity	MET
Walking including shopping	3.5
Hiking/mountain climbing	7
Cycling	4
Gardening	4
Dancing	4.5
Gymnastics	4
Aerobics	6
Roller skating	7
Swimming	8
Jogging	7
Football/basketball/handball	6
Rowing	7
Skiing	7
Boxing	9
Table tennis/badminton	4.5
Tennis	9
Home exercise	7

- **Walk Time:** stratified by gender and height:

Male	**Female**	Time to walk 5 metre criterion for frailty
Height ≤173 cm	Height ≤159 cm	≥7 seconds
Height >173 cm	Height >159 cm	≥6 seconds

- **Grip Strength:** stratified by gender and body mass index (BMI):

Male	Grip strength (kg) criterion for frailty	**Female**	Grip strength (kg) criterion for frailty
BMI ≤ 24	≤29	BMI ≤23	≤17
BMI 24.1–26	≤30	BMI 23.1–26	≤17.3
BMI 26.1–28	≤30	BMI 26.1–29	≤18
BMI >28	≤32	BMI >29	≤21

Table 4.3: Edmonton frailty scale

Domain	Item	Points		
		0	1	2
Cognition	Imagine this pre-drawn circle is a clock. Place the numbers in the correct position and the hands to indicate a time of 11:10.	No errors	Minor spacing errors	Other errors
General health status	How many times have you been admitted to hospital in the past year?	0	1-2	=2
	In general, how would you describe your health?	Good	Fair	Poor
Functional dependence	How many of the following activities do you require help? (meal preparation, shopping, transportation, telephone, housekeeping, laundry, managing money, taking medications)	0-1	2-4	5-8
Social support	When you need help, can you count on someone who is willing and able to meet your needs?	Always	Some-times	Never
Medication use	Do you use ≥ 5 different prescription medications on a regular basis?	No	Yes	-
	Do you forget to take your medications?	No	Yes	-
Nutrition	Have you recently lost weight such that your clothing has become looser?	No	Yes	-
Mood	Do you often feel sad or depressed?	No	Yes	-
Continence	Do you have a problem with losing control of urine when you do not want to?	No	Yes	-
Functional performance	Sit on chair with back and arms resting. When instructed, stand up and walk at a normal pace for 3 meters, then return to chair and sit down.	0-10 sec	11-20 sec	>20sec / unable to complete
Total		0-5 = not frail 6-7 = vulnerable 8-9 = mild frailty 10-11 = moderate frailty 12-17 = severe frailty		

Table 4.4: Deficit index

Items	Cut off
1. Need help preparing meals	Yes = 1, No = 0
2. Need help feeding yourself	Yes = 1, No = 0
3. Need help dressing yourself	Yes = 1, No = 0
4. Need help using the toilet	Yes = 1, No = 0
5. Need help with housekeeping	Yes = 1, No = 0
6. Need help bathing	Yes = 1, No = 0
7. Need help walking	Yes = 1, No = 0
8. Need help using transportation	Yes = 1, No = 0
9. Need help getting in and out of bed	Yes = 1, No = 0
10. Need help managing medications	Yes = 1, No = 0
11. Depend on assistive devices (walker, stick)	Yes = 1, No = 0
12. Dependent on a device for normal breathing	Yes = 1, No = 0
13. Climb 2 flights of stairs without rest	No, unable = 1 Yes, with difficulty = 0.5 Yes, with no difficulty = 0
14. Body mass index	Underweight or obese = 1 Overweight = 0.5 Normal = 0
15. Myocardial infarction	Yes = 1, No = 0
16. Congestive heart failure	Yes = 1, No = 0
17. Diabetes	Yes = 1, No = 0
18. Peripheral vascular disease	Yes = 1, No = 0
19. Cerebrovascular disease	Yes = 1, No = 0
20. Dementia	Yes = 1, No = 0
21. Chronic obstructive pulmonary disease	Yes = 1, No = 0
22. Peptic ulcer disease	Yes = 1, No = 0
23. Hemiplegia/paraplegia	Yes = 1, No = 0
24. Moderate/ severe renal disease	Yes = 1, No = 0
25. Moderate/severe liver disease	Yes = 1, No = 0
26. Any malignancy	Yes = 1, No = 0
27. Metastatic solid tumor	Yes = 1, No = 0
28. Rheumatologic disease	Yes = 1, No = 0
29. Hypertension	Yes = 1, No = 0
30. Hyperlipidemia	Yes = 1, No = 0
31. Depression	Yes = 1, No = 0
32. Anaemia	Yes = 1, No = 0

Physical tests

Reduced muscle strength as evidenced by weak grip strength or slow walking speed, is central to the syndrome of frailty and independently associated with poor outcome (89, 90). In chapters 7 and 8, I evaluated frailty in subjects using the following 3 single physical tests:

1) *Handgrip strength*

   Hand grip strength was obtained with a handgrip dynamometer (Es-100 Ekj107, Evernew, Japan). The subject was seated with forearm resting on the arm of a chair and instructed to hold the dynamometer upright and squeeze as hard as possible. Three trials in the right hand followed by three trials in the left hand were recorded and the highest reading of the 6 was taken as the final reading. Subjects were classified as frail according to the Fried grip strength criterion for frailty (44). (Figure 4.2)

2) *Timed get up and go test (TUGT):*

   The area for the timed get up and go test was set up by measuring 3 meters from the front legs of a straight-backed armchair. The subject was instructed to: "Sit with your back against the chair and your arms on the arm rests. On the word `go,' stand upright, then walk at your normal pace to the line on the floor, turn around, return to the chair, and sit down." The time required to complete the test was time from the word `go' to time when the subject returned to the starting position. Subjects were classified as frail according to the EFS TUGT criterion for frailty (80). Subjects who took more than 10 seconds to complete the test (Table 4.3) or were unable to complete the test due to limitation in mobility were classified as frail.

3) *Five metre walk test (5MWT):*

   The subject was instructed to walk at a normal pace for 5 meters according to their ability. The time required to complete the test was time from the word `go' to time when the subject reached the 5-meter-point. Subjects were classified as frail according to the Fried 5MWT criterion for frailty (44). Subjects who took more than 6-7 seconds (depending on sex and height) to complete the test (Figure 4.2)

or were unable to complete the test due to limitation in mobility were classified as frail.

In Chapter 8, in order to study the relationship between the degree of frailty and outcome, I further stratified patients into 5 categories of 5MWT according to distribution of 5MWT in the cohort; I classified those with 5MWT ≤7.0 sec as non-frail; those with 5MWT 7.0-9.5 sec, 10.0-14.5 sec, 15.0-28.0 sec, I classified as pre-frail, mildly and moderately frail respectively; those who were unable to complete 5MWT, I classified as severely frail.

4.3.6 Malnutrition evaluation

Simple screening tools

In Chapters 5, 6, 9 and 10, I screened subjects for malnutrition using the following 3 simple screening tools. These tools took into account laboratory tests and anthropometric measures and could be completed within a minute.

1) *The COntrolling NUTritional Status score* (CONUT; measured between 0-12): CONUT score was developed by Ignacaio de Ulibarri and colleagues in 2005 as a screening tool for assessment of nutritional status of inpatients (131). It uses serum albumin, cholesterol and total lymphocyte count (Table 4.5a). Subjects with a CONUT score 0-1 were classified as having normal nutritional status, those with CONUT score 2-4, 5-8, 9-12 were classified as having mild, moderate and severe malnutrition respectively (131). Subjects with CONUT score ≥2 were classified as malnourished (131).

Table 4.5a: COntroling NUTritional Status score.

	Degree of malnutrition			
	Normal	**Mild**	**Moderate**	**Severe**
Albumin, g/L (score)	≥35 (0)	30-34 (2)	25-29 (4)	<25 (6)
Cholesterol, mmol/L (score)	>4.65 (0)	3.62-4.65 (1)	2.59-3.61 (2)	<2.59 (3)
Total Lymphocyte count, $x10^9$/L (score)	≥1.60 (0)	1.20-1.59 (1)	0.80-1.19 (2)	<0.80 (3)
Overall score	0-1	2-4	5-8	9-12

2) *The geriatric nutritional risk index* (GNRI):

GNRI screens for malnutrition using serum albumin level and the ratio of body weight to ideal body weight (133). Ideal body weight was calculated using the formula: 22 x square of height in meters (146). GNRI was calculated using the formula: [1.489 x albumin (g/L)] + [41.7 x current weight/ ideal weight] (133). (Table 4.5b) Subjects with GNRI >98 were classified as having normal nutritional status, those with GNRI 92-98, 82-91, <82 were classified as having mild, moderate and severe malnutrition respectively (133). Subjects with GNRI ≤ 98 were classified as malnourished (133).

Table 4.5b: Geriatric nutritional risk index.

	Degree of malnutrition			
	Normal	**Mild**	**Moderate**	**Severe**
1.489 x serum albumin (g/L) + 41.7 x (body weight / ideal body weight)	>98	92-98	82-91	<82

3) *The prognostic nutritional index* (PNI):

PNI is another nutritional screening tool, calculated using the formula: 10 x serum albumin (g/dL) + 0.005 x total lymphocyte count (mm^3) (132, 147). Subjects with PNI >38 were classified as having normal nutritional status; those with PNI 35-38 and <35 were classified as having moderate and severe malnutrition

respectively (132, 147). (Table 4.5c) There is no 'mild' category of malnutrition according to PNI. Subjects with PNI ≤38 were classified as malnourished (132, 147).

Table 4.5c: Prognostic nutritional index.

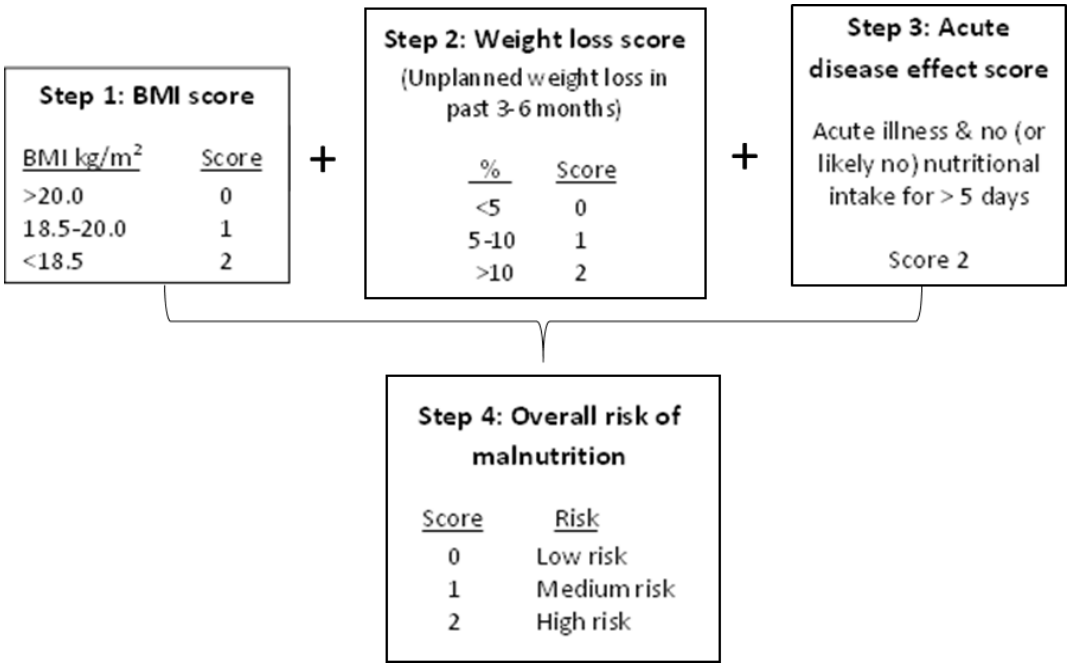
	Degree of malnutrition			
	Normal	**Mild**	**Moderate**	**Severe**
10 x serum albumin (g/dL) + 0.005 x total lymphocyte count (mm^3)	>38	-	35-38	<35

Multi-dimensional screening tools

In chapters 9 and 10, I also evaluated malnutrition using the following 3 multi-dimensional tools. These tools take into account various factors that affect nutritional status including: the effect of acute illness, mobility, co-morbidities and dietary intake. They are more time consuming to perform (5-20 minutes, depending on mobility of patients).

1) *Malnutrition Universal Screening Tool (*MUST; measured between 0-2):
   MUST is a screening tool developed by the Malnutrition Advisory Group of the British Association for Parenteral and Enteral Nutrition in 2003 to identify malnutrition in adults (136). MUST uses 3 simple steps: BMI, weight loss and the effect of acute illness on food intake to generate an overall risk of malnutrition (Figure 4.3). Subjects with MUST score 0 were classified as having normal nutritional status (low malnutrition risk); those with MUST score 1 and ≥ 2 were classified as having mild (medium risk) and ≥ moderate (high risk) malnutrition respectively (136). Subjects with MUST ≥ 1 were classified as malnourished (136). I completed the BAPEN's e-learning available at www.bapen.org.uk before performing assessments on patients.

Figure 4.3: Malnutrition universal screening tool.



2) Mini Nutritional Assessment Short Form (MNA-SF; measured between 0-14):

MNA was developed in 1996 as a tool to identify malnutrition in elderly patients (137). MNA-short form (MNA-SF), a shorter version of MNA, consists of 6 questions which assess food intake, weight loss, mobility, acute events, neuro-psychological problems and BMI (148). (Table 4.6) Subjects with MNA-SF score 12-14 were classified as having normal nutritional status, those with MNA-SF score 8-11 and ≤7 were classified as having mild and ≥ moderate malnutrition respectively (148). Subjects with MNA-SF score ≤11 were classified as malnourished (148).

Table 4.6: Mini Nutritional Assessment Short Form.

Questions	Score
Decline in food intake over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties	0 = severe decrease 1 = moderate decrease 2 = no decrease
Psychological stress or acute disease during the last 3 months	0 = no 2 = yes
Neuro-psychological problems	0 = severe dementia/ depression 1 = mild dementia 2 = no psychological problems
Weight loss during the last 3 months	0 = >3kg 1 = does not know 2 = 1-3 kg 3 = no weight loss
Mobility	0 = bed/ chair bound 1 = able to get out of bed/chair but does not go out 2 = goes out
Body mass index	0 = <19 1 = 19-21 2 = 21-23 3 = ≥ 23
Total score	12-14 = normal nutrition status 8-11 = at risk of malnutrition 0-7 = malnourished

3) *Subjective global assessment* (SGA; measured between A-C)*:*

SGA is a nutrition evaluation tool that is widely used in a variety of clinical settings (138, 149). It includes an assessment of medical history (specifically evaluating weight loss, changes in dietary intake, gastrointestinal symptoms and functional capacity) and a physical examination (specifically evaluating large muscle wasting as determined by palpable loss of bulk; subcutaneous fat loss as determined by arm circumference; peripheral oedema and ascites: graded as none; mild to moderate or severe) (Table 4.7). The measurements were not precise, but are a subjective impression. Each component of the SGA was ranked as either 'A', 'B' or 'C' according to specific set criteria, with 'A' reflecting normal nutritional status and 'C' reflecting significant malnutrition (138). The ranking with the

highest frequency amongst individual components of SGA was determined as the overall SGA score. Subjects with SGA- A were classified as having normal nutritional status, those with SGA-B and C, were classified as having mild and ≥ moderate malnutrition respectively (138). Subjects with SGA-B or C were classified as malnourished (138).

Table 4.7: Subjective global assessment.

		SGA categories		
		A	B	C
Medical history				
Weight change	Past 6 months	↓<5%	↓5-10%	↓>10%
	Past 2 weeks	↑ or no change (normal weight)	No change (below normal weight)	↓
Diet	Change	No change; adequate	No change; inadequate	
	Intake	Intake borderline; increasing	Intake borderline, decreasing Intake poor, increasing	Intake poor; no change Intake poor; decreasing
	Type	-	Suboptimal diet; Full liquid	Hypocaloric liquid; Starvation
Symptoms	Nausea Vomiting Diarrhoea Anorexia	None; intermittent	Some (daily < 2 weeks)	All (daily > 2 weeks)
Functional capacity	Mobility	No dysfunction	Difficulty with ambulation/ normal activities	Bed/chair ridden
	Change in mobility	Improved	No change	Regressed

Table 4.7 (continued): Subjective global assessment.

		SGA categories		
		A	B	C
Physical examination				
Subcutaneous fat	Under eyes	Slightly bulging		Hollowing, depression, dark circles
	Triceps	Large space between fingers		Very little space between fingers, or fingers touch
	Biceps	Large space between fingers		Very little space between fingers, or fingers touch
Muscle wasting	Temple	Well-defined muscle/ flat	Slight depression	Hollowing, depression
	Clavicle	Not visible in males, may be visible but not prominent in females	Some protrusion, may not be all the way along	Protruding/ prominent bone
	Shoulder	Rounded	No square look, acromion process may protrude slightly	Square look, bones prominent
	Scapula/ribs	Bones not prominent; no significant depressions	Mild depressions or bone may show slightly; not all areas	Bones prominent; significant depressions
	Quadriceps	Well rounded; no depressions	Mild depression	Significant depression; thin
	Calf	Well developed		Thin; no muscle definition
	Knee	Bones not prominent		Bones prominent
	Interosseous muscle between thumb and forefinger	Muscle protrudes; could be flat in females		Flat or depressed area

Table 4.7 (continued): Subjective global assessment.

		SGA categories		
		A	B	C
Physical examination				
Oedema	Related to malnutrition	No sign	Mild to moderate	Severe
Ascites	Related to malnutrition	No sign	Mild to moderate	Severe
Overall SGA rating		**A**	**B**	**C**

Laboratory tests

Biochemical and immunological tests such as serum cholesterol, albumin and total lymphocyte count, have been demonstrated to be related to nutritional status (150). In Chapters 9 and 10, I evaluated malnutrition in subjects using the following 3 laboratory tests. These tests are based on the components of CONUT score and have been studied in prior work (151).

1) *Serum cholesterol level (mmol/L):*

Subjects with serum cholesterol level >4.65 were classified as having normal nutritional status according to the CONUT score cut-off, those with serum cholesterol level 3.62-4.65, 2.59-3.61, <2.59 were classified as having mild, moderate and severe malnutrition respectively (131). (Table 4.5a) Subjects with serum cholesterol level ≤ 4.65 were classified as malnourished (131).

2) *Serum albumin level (g/L):*

Subjects with serum albumin level ≥35 were classified as having normal nutritional status according to the CONUT score cut-off, those with serum albumin level 30-34, 25-29 and <25 were classified as having mild, moderate and

severe malnutrition respectively (131). (Table 4.5a) Subjects with serum albumin level <35 were classified as malnourished (131).

3) Serum total lymphocyte count ($x10^9/L$):

Subjects with serum total lymphocyte count of ≥1.6 were classified as having normal nutritional status according to the CONUT score cut-off, those with total lymphocyte count 1.20-1.59, 0.80-1.19 and <0.80 were classified as having mild, moderate and severe malnutrition respectively (131). (Table 4.5a) Subjects with serum total lymphocyte count <1.6 were classified as malnourished (131).

4.3.7 Body composition analysis

In Chapter 10, a subset of subjects provided informed consent for further body composition analysis. Body composition assessment was performed using the Body composition analyser (BCA): Tanita MC-180 MA scales (Tanita Europe BV, the Netherlands). Subjects who had poor mobility, severe symptoms and pacemakers or defibrillators were excluded (152).

Body composition is estimated by bioelectric impedance. BCA uses the principle that the amount of electricity that can be conducted through a conductor is directly proportional to the concentrations of ions contained within it. For example, conductivity of blood and urine is high, that of muscle is intermediate and that of tissues such as bone, fat or air is low (152).

Subjects were instructed to wear light clothes and stand bare-foot on the scales, with both feet on the foot electrodes and both hands holding the handles with electrodes. A current is transmitted between the surface electrodes. BCA measures body water, which is then used to estimate fat-free mass and subtracting this value from weight, estimates body fat (152). Weight, BMI and body composition (including fat mass percentage, muscle mass percentage, total body water, extracellular water (ECW), intracellular water (ICW), ratio between extracellular and intracellular water (ECW/ICW) and impedance) were determined.

4.4 End points and follow up

The primary end point for all studies in this thesis was all-cause mortality. In Chapters 8 and 10, the secondary end point was the combination of all-cause hospitalisation and all-cause mortality. The length of follow up will be detailed in individual chapters.

Mortality was ascertained by using primary and secondary care medical records (updated systematically using a NHS electronic database), autopsy reports and death certificates. The cause of death reported in this thesis was the primary cause of death recorded on the medical record/ death certificate. For patients who died out of hospital, the cause of death was adjudicated by the medical team based on previous medical records, recent hospitalisations and medical encounters. Cardiovascular deaths included deaths caused by MI, progression of HF, ventricular arrhythmias and CVD. Other deaths were regarded as non-cardiovascular and included deaths secondary to infection, malignancies and end-stage co-morbidities.

Hospitalisation was ascertained by using electronic medical records and discharge letters. Hospitalisations referred to non-elective admissions to hospital with length of stay of at least 24 hours. The cause of hospitalisation reported in this thesis was the *primary* cause of hospitalisation recorded on discharge letters. Cardiovascular hospitalisations included hospitalisations secondary to decompensated HF, ACS, arrhythmias, CVD and PVD. Other hospitalisations were regarded as non-cardiovascular.

4.5 Statistical analysis

I expressed continuous data as mean with standard deviation (SD) if normally distributed and median with interquartile range (IQR) (25^{th} to 75^{th} centiles) if not normally distributed. I expressed categorical data as n (%). I used normal distribution curves to assess normality of continuous variables.

I used independent t-tests to compare two means if the distribution was normal and variances were uniform. If these criteria were not met, I used the Mann Whitney U test. To compare more than two means, I used one-way analysis of variances (ANOVA) if the

distribution was normal and variances were uniform. If these criteria were not met, I used the Kruskal-Wallis test. I used the chi-squared test to compare proportions between groups.

I used Pearson's correlation coefficient to assess the relationship between two variables when the variables are linearly-related and approximately normally distributed, with no significant outliers. I visually inspected the scatter plot to check for linearity. If the above criteria were not met, I used Spearman correlation coefficient. I used logistic regression analysis to estimate the association between a binary dependent variable and other independent variables.

I presented time-to-event data graphically using Kaplan-Meier curves (153). I used log-rank-tests to compare survival between groups. I performed univariable and multivariable analyses with Cox proportional hazard regression to determine significant predictors of events. I applied log-transformation when the data were very skewed.

Model discrimination refers to the ability of a model to distinguish subjects experiencing an outcome from those who did not. I constructed base models for predicting outcomes using variables associated with the outcome. I then added further variables of interest into the base models. I used Harrell's C-statistic and log-likelihood ratio (LLR) or net reclassification index (NRI) to evaluate model discrimination in survival analysis, whilst noting the Harrell's C-statistic is overoptimistic for censored survival data (154, 155). The C-statistic (the area under the Receiver Operating Characteristic curve) is the probability that predictions and outcomes are concordant (the same). A C-statistic of 0.5 means that the relationship is no better than chance (i.e. no discriminative ability), while a C-statistic of 1 indicates perfect discrimination. The more negative the LLR, the bigger the improvement in model discrimination from addition of variables to the base models.

A two-tailed P-value of <0.05 was considered significant in all analyses. All statistical analyses were performed using SPSS 23-25 (SPSS INc.,Chicago, IL, USA) and The Stata (14^{th} Version, StataCorp, TX, USA) statistical computer package.

4.6 Ethics

All studies conformed to the principles outlined in the Declaration of Helsinki. All subjects have given written informed consent for their data to be used for research. The study detailed in Chapter 5 has been approved by The Research and Development Department at Diana, Princess of Wales Hospital, Grimsby, UK. The studies detailed in Chapters 6-12 have been approved by The Research and Development Department at Castle Hill Hospital, Hull, UK.

4.7 Conclusion

This chapter discussed the aims of this thesis and the general methodology of a series of studies I performed to achieve such aims. In Chapters 5 to 12, I will describe the execution and key findings of each study in detail.

Chapter 5 Prevalence, Clinical Associations and Prognostic Significance of Frailty and Malnutrition in Patients with Acute Heart Failure

5.1 Chapter summary

Background: Frailty and malnutrition may be common in patients with AHF and associated with adverse outcomes, but few data exist.

Objective: To study the prevalence and prognostic significance of frailty and malnutrition in patients admitted acutely to hospital with HF.

Methods: I enrolled 265 consecutive patients (62% males, median age: 80 (IQR: 72-86) years, median NT-proBNP 3633 (IQR: 2025-6407) ng/L) admitted with HF due to LVSD between 2013 and 2014. I screened patients for frailty using Derby frailty index (DFI), the Acute Frailty Network criteria (AFN) and Clinical frailty scale (CFS); and for malnutrition using the COntroling NUTritional Status (CONUT) score, Geriatric nutritional risk index (GNRI) and Prognostic nutritional index (PNI).

Results: According to the DFI, AFN and CFS (>4), 50%, 53% and 53% patients were frail respectively. According to the CONUT score (>4), GNRI (≤98) and PNI (≤38), 46%, 46% and 42% patients were malnourished respectively.

During a median follow-up of 598 days (IQR: 319-807 days), 113 patients died. 1-year mortality was 1% for those who were neither frail nor malnourished; 15% for those who were either malnourished or frail; and 65% for those who were both malnourished and frail.

Amongst the malnutrition tools, PNI; and amongst the frailty tools, CFS, increased model performance most compared with base model. A final model including CFS and PNI increased Harrell's C-statistic for mortality prediction from 0.68 to 0.84.

Conclusion: Frailty and malnutrition are common in patients hospitalised with HF. Worsening frailty and malnutrition as determined by screening tools are strongly related to worse outcome.

5.2 Introduction

Admission to hospital for HF is very common, as is subsequent re-admission (4, 5). Not only is hospitalisation expensive, each admission is associated with a worse prognosis (4, 5). Modern medical therapy for patients with CHF is based on the results from large, RCTs, yet the patients included in trials often poorly reflect the reality of patients in clinical practice (21). The median age of patients admitted to hospital with HF in the UK is 81 years (4). Elderly patients with HF usually have complex co-morbidities and clinical features distinct from subjects enrolled in major clinical trials conducted in HF. Frailty and malnutrition are two common features in patients with HF which are often overlooked (156, 157).

Screening HF patients for malnutrition and frailty might be helpful in identifying at-risk patients. Although many tools for frailty and malnutrition exist, there is no consensus as to which tool is best to use in patients with HF (156, 157). Amongst malnutrition screening tools, the COntrolling NUTritional status **(**CONUT) score, the prognostic nutritional index (PNI) and the geriatric nutritional risk index (GNRI) are the most widely studied in HF populations (157). Amongst frailty screening tools, the CFS is popular and widely used (84); while the Derby frailty index (DFI) and the Acute Frailty Network (AFN) frailty criteria are simple frailty identification tools developed recently (85-87).

In this chapter, I will study the prevalence of frailty and malnutrition and their relation to outcome in patients admitted to hospital with HF.

5.3 Methods

5.3.1 Study population

I prospectively enrolled 265 consecutive patients admitted to a district hospital (Diana, Princess of Wales Hospital) in Grimsby, UK, between January 2013 and December 2014 with a primary diagnosis of HF with LVSD. All patients had a full medical history, physical examination and blood tests within a few hours of admission. A detailed description of the study population can be found in Chapter 4.

5.3.2 Frailty evaluation

I evaluated frailty in patients using the following 3 screening tools:

1) Derby frailty index (DFI)
2) Acute Frailty Network criteria (AFN)
3) Clinical frailty scale (CFS)

A description of the frailty evaluation process can be found in the 'frailty evaluation' section in Chapter 4.

5.3.3 Malnutrition evaluation

I evaluated malnutrition in patients using the following 3 simple tools:

1) COntroling NUTritional Status (CONUT) score
2) Geriatric nutritional risk index (GNRI)
3) Prognostic nutritional index (PNI)

A detailed description of the malnutrition evaluation process can be found in the 'malnutrition evaluation' section in Chapter 4.

5.3.4 End point and follow up

I followed the patients until the 1st of February 2016 and the primary end point was all-cause mortality.

5.3.5 Statistical analysis

Routine statistical analyses have been detailed in Chapter 4. Firstly, I studied the prevalence of frailty and malnutrition. Next, I used Venn diagrams to illustrate the

relationship between frailty and malnutrition tools. I then used Pearson's correlation coefficients with scatter plots to assess the correlations between frailty and malnutrition tools. Finally, I explored the relation between frailty, malnutrition and mortality using Cox proportional hazards regression.

In order to further assess the prognostic value of the frailty and malnutrition tools, I created two base models for predicting mortality:

1) Malnutrition base model

   Variables included were: age, sex, Hb, AF, log [NT-proBNP], creatinine, sodium, recurrent falls and IHD.

2) Frailty base model

   Variables included were: sex, Hb, AF, log [NT-proBNP], creatinine, sodium and IHD. I excluded age and recurrent falls from the frailty base model as they are part of the DFI and AFN.

I then added each of the frailty and malnutrition tools in turn to their specific base models and used Harrell's C-statistic to evaluate model discrimination. I used the frailty and malnutrition tools with the highest Harrell's C-statistic to construct a final model for predicting mortality.

Using the best frailty and malnutrition tools, I stratified the cohort into 4 groups:

1) Frail and malnourished
2) Frail but not malnourished
3) Malnourished but not frail
4) Neither malnourished nor frail

I then constructed Kaplan-Meier curves to compare survival amongst the 4 groups.

5.4 Results

5.4.1 Baseline characteristics

Baseline characteristics of the entire cohort and frail versus (vs) non-frail patients are shown in Table 5.1a. Baseline characteristics of malnourished vs non-malnourished patients are shown in Table 5.1b.

Table 5.1a: Baseline characteristics of frail vs non-frail patients by CFS.

	HF patients N=265	**Frail** CFS >4 N=139	**Non-frail** CFS ≤4 N=126	**P** (Frail vs non frail)
Demographics				
Age (years)	80 (72-86)	85 (80-89)	73 (66-79)	<0.001
Age >75 (years), n (%)	176 (66)	122 (88)	54 (43)	<0.001
Sex (male), n (%)	164 (62)	82 (59)	83 (66)	0.2
Nursing home, n (%)	37 (14)	37 (27)	0	<0.001
BP systolic (mmHg)	123 (109-140)	123 (109-140)	122 (109-139)	0.9
HR (bpm)	83 (68-97)	82 (66-96)	84 (72-98)	0.4
QRS duration (ms)	108 (96-134)	110 (96-135)	107 (96-124)	0.4
Weight (kg)	78 (65-90)	73 (62-85)	84 (70-94)	<0.001
BMI (kg/m^2)	28 (23-31)	26 (22-30)	28 (25-33)	0.02
NYHA III/IV, n (%)	196 (74)	117 (84)	79 (63)	0.001
Co-morbidities				
AF, n (%)	146 (55)	93 (67)	53 (42)	<0.001
HTN, n (%)	167 (63)	96 (69)	71 (56)	0.03
IHD, n (%)	115 (43)	66 (48)	49 (39)	0.2
Valvular disease, n (%)	85 (32)	57 (41)	28 (22)	0.001
Diabetes Mellitus, n (%)	94 (36)	43 (31)	51 (41)	0.1
COPD, n (%)	59 (22)	34 (25)	25 (20)	0.4
Depression, n (%)	46 (17)	28 (20)	18 (14)	0.2
Falls, n (%)	117 (44)	101 (73)	16 (13)	<0.001
Dementia, n (%)	47 (18)	46 (33)	1 (1)	<0.001
Charlson Score	8 (6-10)	9 (7-11)	7 (5-9)	0.001

Table 5.1a (continued): Baseline characteristics of frail vs non-frail patients by CFS.

	Total cohort N=265	**Frail** CFS >4 N=139	**Non-frail** CFS ≤4 N=126	**P** (Frail vs non frail)
Medications				
ACEi/ARB, n (%)	170 (64)	80 (58)	90 (71)	0.02
BB, n (%)	198 (75)	96 (69)	102 (81)	0.03
MRA, n (%)	113 (43)	53 (38)	60 (48)	0.1
Loop diuretics, n (%)	226 (85)	124 (89)	102 (81)	0.06
Thiazide diuretics, n (%)	6 (2)	2 (1)	4 (3)	0.3
Digoxin, n (%)	54 (20)	32 (23)	22 (18)	0.3
Statin, n (%)	144 (54)	68 (49)	76 (60)	0.06
Blood tests				
NT-ProBNP (ng/L)	3633 (2025-6407)	3669 (1899-6579)	3537 (2091-6097)	0.8
Hb (g/dL)	12.4 (11.1-13.8)	11.8 (10.5-13.0)	13.4 (12.0-14.2)	<0.001
Urea (mmol/L)	8.9 (6.4-13.2)	11.1 (7.3-16.2)	7.6 (5.8-10.9)	<0.001
Creatinine (µmol/L)	105 (83-141)	118 (89-156)	98 (77-117)	0.008
Sodium (mmol/L)	138 (135-140)	137 (134-139)	138 (135-140)	0.1
Potassium (mmol/L)	4.2 (3.9-4.65)	4.3 (3.9-4.7)	4.2 (3.9-4.5)	0.05
Albumin (g/L)	33 (29-36)	30 (27-34)	35 (32-37)	<0.001
Cholesterol (mmol/L)	4.0 (3.4-4.7)	3.9 (3.3-4.6)	4.2 (3.6-4.9)	0.2
Lymphocyte ($x10^9$/L)	1.2 (0.8-1.7)	1.0 (0.7-1.4)	1.5 (1.1-2.0)	<0.001

Table 5.1b: Baseline characteristics of malnourished vs non-malnourished patients by PNI.

	Malnourished PNI ≤38 N=113	**Non-malnourished** PNI >38 N =152	**P** (mal vs non-mal)
Demographics			
Age (years), n (%)	84 (77-89)	78 (69-84)	<0.001
Age >75 (years), n (%)	85 (75)	91 (60)	0.009
Sex (male), n (%)	71 (63)	93 (61)	0.8
Nursing home resident, n (%)	31 (27)	6 (4)	<0.001
NYHA III/IV, n (%)	92 (81)	104 (68)	0.03
BP systolic (mmHg)	120 (107-138)	125 (110-141)	0.1
HR (bpm)	83 (69-100)	82 (66-96)	0.5
QRS duration (ms)	106 (94-137)	110 (97-127)	0.3
Weight (kg)	71 (59-85)	82 (70-93)	0.002
BMI (kg/m^2)	26 (21-30)	28 (25-32)	0.03
Co-morbidities			
AF, n (%)	70 (62)	76 (50)	0.05
HTN, n (%)	73 (65)	94 (62)	0.6
IHD, n (%)	51 (45)	64 (42)	0.6
Valvular disease, n (%)	50 (44)	35 (23)	<0.001
Diabetes Mellitus, n (%)	34 (30)	60 (40)	0.1
COPD, n (%)	27 (24)	32 (21)	0.6
Depression, n (%)	19 (17)	27 (18)	0.8
Falls, n (%)	71 (63)	46 (30)	<0.001
Dementia, n (%)	29 (26)	18 (12)	0.004
Charlson Score	8 (6-11)	8 (6-10)	0.6

Table 5.1b (continued): Baseline characteristics of malnourished vs non-malnourished patients by PNI.

	Malnourished PNI ≤38 N=113	**Non-malnourished** PNI >38 N =152	**P** (Mal vs non-mal)
Medications			
ACEi/ARB, n (%)	61 (54)	109 (72)	0.003
BB, n (%)	77 (68)	121 (80)	0.03
MRA, n (%)	48 (43)	65 (43)	0.9
Loop diuretics, n (%)	99 (88)	127 (84)	0.4
Thiazide diuretics, n (%)	2 (2)	4 (3)	0.6
Digoxin, n (%)	24 (21)	30 (20)	0.8
Statin, n (%)	54 (48)	90 (59)	0.07
Blood tests			
NT-ProBNP (ng/L)	4198 (2230-7966)	3322 (1514-5600)	0.1
Hb (g/dL)	11.8 (10.5-13)	13.2 (11.6-14.1)	<0.001
Urea (mmol/L)	11.7 (7.1-17)	8 (6.1-11.6)	0.001
Creatinine (µmol/L)	115 (85-158)	100 (82-126)	0.06
Sodium (mmol/L)	137 (133-139)	138 (135-140)	0.008
Potassium (mmol/L)	4.3 (3.9-4.8)	4.2 (3.9-4.5)	0.1
Albumin (g/L)	28 (26-30)	35 (34-37)	<0.001
Cholesterol (mmol/L)	3.9 (3.2-4.6)	4.1 (3.6-4.8)	0.1
Lymphocyte ($x10^9$/L)	0.9 (0.6-1.2)	1.6 (1.1-2.1)	<0.001

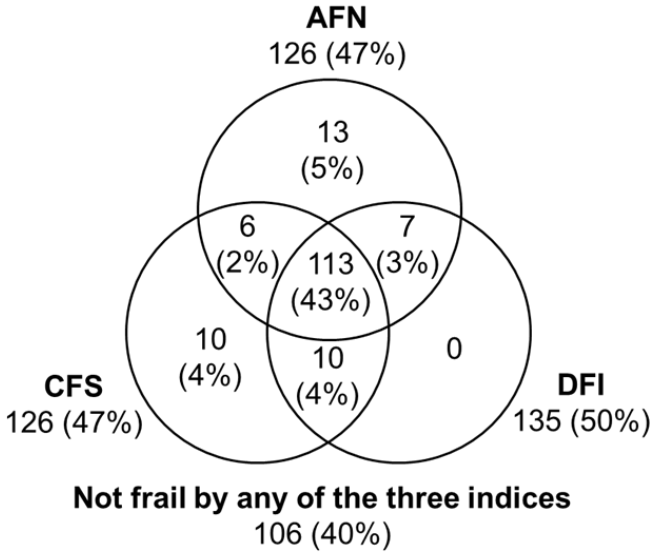
NYHA = New York Heart Association Class, BP = blood pressure, HR= heart rate, BMI= body mass index, AF= atrial fibrillation, HTN= hypertension, IHD = Ischaemic heart disease, COPD = Chronic obstructive pulmonary disease, ACEi/ARB = Angiotensin-converting enzyme inhibitor or Angiotensin receptor blocker, MRA = Mineralocorticoids receptor antagonists, BB= beta-blockers, NT-proBNP = N-terminal Pro Brain Natriuretic Peptide, Hb = Haemoglobin, PNI = prognostic nutritional index, CFS = Clinical Frailty Scale.

The majority of patients were male (62%) and elderly (median age: 80 (IQR: 72-86) years). 74% of patients had NYHA class III/IV symptoms and median NT-proBNP was 3633 (IQR: 2025-6407) ng/L. Around half of the cohort was ‘frail’ or ‘malnourished’.

5.4.2 Prevalence and clinical associations of frailty and malnutrition

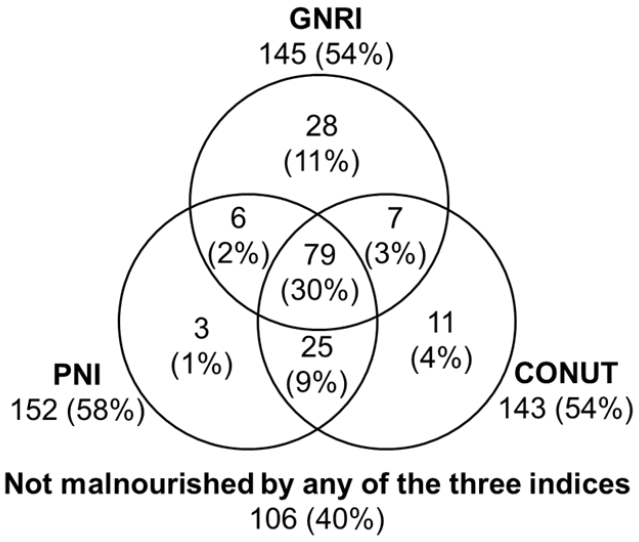
According to the DFI, AFN and CFS (>4), 50%, 53% and 53% were frail respectively; 43% (N=113) were classified as frail by all 3 frailty tools (Figure 5.1).

Figure 5.1: Prevalence of frailty by DFI, AFN and CFS.



According to the CONUT score (>4), GNRI (≤98) and PNI (≤38), 46%, 46% and 42% patients were malnourished respectively; 30% (N=79) were classified as malnourished by all 3 malnutrition tools (Figure 5.2).

Figure 5.2: Prevalence of malnutrition by CONUT, GNRI and PNI.



Frail and malnourished patients were older; more likely to be nursing home residents; more likely to suffer from recurrent falls, dementia, anaemia and AF; had lower BMI, worse symptoms and renal function; and were less likely to be on an ACEi/ ARB or a beta-blocker. (Table 5.1a and 5.1b)

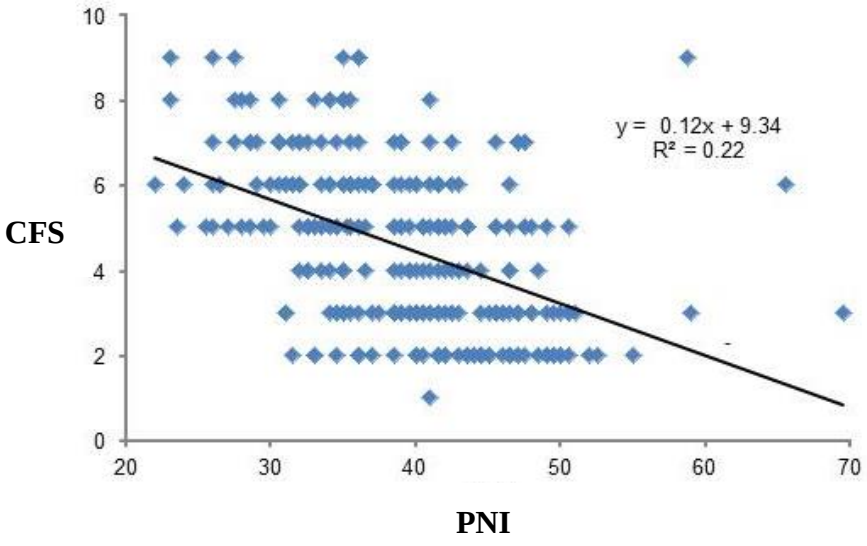
Frailty and malnutrition tools correlated with each other (Table 5.2). Figure 5.3 shows the relationship between CFS and PNI. Although increasing frailty correlated with worsening malnutrition, the correlation was weak (coefficient of determination, $R^2 = 0.22$, $P<0.001$).

Table 5.2: Correlation coefficients for frailty and malnutrition tools.

Tools	DFI	AFN	CFS	CONUT	GNRI
AFN	0.78				
CFS	0.70	0.61			
CONUT	0.46	0.40	0.50		
GNRI	-0.34	-0.30	-0.39	-0.58	
PNI	-0.43	-0.38	-0.47	-0.85	0.55

All p values < 0.001.
CONUT= Controlling nutritional index, GNRI = Geriatric Nutritional Risk Index, PNI = Prognostic Nutritional Index, AFN = Acute Frailty Network Frailty criteria, CFS = Clinical Frailty Scale, DFI = Derby Frailty Index

Figure 5.3: Relationship between CFS and PNI.



5.4.3 Frailty and malnutrition: associations with mortality

During a median follow-up of 598 days (IQR: 319-807 days), 113 patients died. Univariable predictors of mortality are shown in table 5.3. Worsening frailty and malnutrition were both associated with worse outcome.

Table 5.3: Univariable analysis of factors predicting all-cause mortality.

Worse outcome per unitary increase	**HR (95%CI)**	**Wald χ^2**	**P**
Age (years)	1.05 (1.03-1.07)	23.0	<0.001
Sex (male vs female)	0.92 (0.63-1.36)	1.6	0.7
Hb (g/dL)	0.85 (0.78-0.94)	11.2	0.001
AF (Y vs N)	1.97 (1.32-2.92)	11.2	0.001
Log [NT-ProBNP]	1.92 (1.16-3.16)	6.5	0.01
Creatinine (per 10 µmol/L)	1.02 (1.01-1.05)	9.6	0.002
Sodium (mmol/L)	0.95 (0.93-0.98)	8.8	0.003
Recurrent Falls (Y vs N)	4.89 (3.19-7.51)	52.7	<0.001
IHD (Y vs N)	1.50 (1.03-2.17)	4.5	0.03
CONUT score (increasing score)	1.42 (1.32-1.53)	91.4	<0.001
GNRI (decreasing score)	1.04 (1.03-1.06)	40.5	<0.001
PNI (decreasing score)	1.14 (1.12-1.17)	88.4	<0.001
AFN (frail vs non-frail)	6.46 (3.90-10.70)	52.3	<0.001
CFS (increasing score)	1.74 (1.57-1.93)	109.0	<0.001
DFI (frail vs non-frail)	9.23 (5.43-15.69)	67.2	<0.001

HR = hazard ratio, CI= confidence interval, χ^2= chi-square, CONUT= controlling nutritional index, GNRI = Geriatric Nutritional Risk Index, PNI = Prognostic Nutritional Index, AFN = Acute Frailty Network Frailty criteria, CFS = Clinical Frailty Scale, DFI = Derby Frailty Index, Hb = Haemoglobin, IHD = ischaemic heart disease, NT-proBNP = N-terminal Pro Brain Natriuretic Peptide, AF= atrial fibrillation, Y = yes, N=no.

Of the variables that were significant in univariable analysis (excluding 3 malnutrition tools, age and recurrent falls, which are included in AFN and DFI), CFS and DFI were significant predictors of mortality in a multivariable model for frailty tools (Table 5.4a).

Table 5.4a: Multivariable analysis of frailty tools predicting all-cause mortality.

Worse outcome per unitary increase	HR (95%CI)	Wald χ^2	P
Sex (male vs female)	0.78 (0.52-1.18)	1.4	0.2
Hb (g/dL)	0.97 (0.87-1.08)	0.3	0.6
AF (Y vs N)	1.10 (0.72-1.67)	0.2	0.7
Log [NT-ProBNP]	1.62 (0.97-2.71)	3.5	0.06
Creatinine (per 10 µmol/L)	1.03 (1.00-1.05)	3.2	0.07
Sodium (mmol/L)	0.97 (0.94-1.01)	2.1	0.2
IHD (Y vs N)	1.12 (0.74-1.68)	0.3	0.6
AFN (frail vs non-frail)	1.10 (0.50-2.44)	0.1	0.8
CFS (increasing score)	1.56 (1.35-1.81)	35.8	<0.001
DFI (frail vs non-frail)	2.58 (1.09-6.12)	4.6	0.03

Table 5.4b: Multivariable analysis of malnutrition tools predicting all-cause mortality.

Worse outcome per unitary increase	HR (95%CI)	Wald χ^2	P
Age (years)	1.02 (0.99-1.04)	2.2	0.1
Sex (male vs female)	0.82 (0.54-1.24)	0.9	0.3
Hb (g/dL)	1.07 (0.96-1.20)	1.4	0.2
AF (Y vs N)	1.21 (0.79-1.87)	0.8	0.4
Log [NT-ProBNP]	1.16 (0.72-1.87)	0.4	0.5
Creatinine (per 10 µmol/L)	1.02 (1.01-1.05)	3.7	0.05
Sodium (mmol/L)	0.96 (0.93-1.00)	4.5	0.03
Recurrent Falls (Y vs N)	2.60 (1.60-4.24)	14.7	<0.001
IHD (Y vs N)	1.34 (0.89-2.00)	2.0	0.2
CONUT score (increasing score)	1.06 (0.89-1.27)	0.4	0.5*
GNRI (decreasing score)	1.01 (1.00-1.03)	1.0	0.3
PNI (decreasing score)	1.08 (1.01-1.16)	4.4	0.04*

HR = hazard ratio, CI= confidence interval, χ^2= chi-square, AFN = Acute Frailty Network Frailty criteria, CFS = Clinical Frailty Scale, DFI = Derby Frailty Index, CONUT= controlling nutritional index, GNRI = Geriatric Nutritional Risk Index, PNI = Prognostic Nutritional Index, Hb = Haemoglobin, IHD = ischaemic heart disease, NT-proBNP = N-terminal Pro Brain Natriuretic Peptide, AF= atrial fibrillation, Y = yes, N=no.

* As increasing CONUT score is highly correlated with decreasing PNI (correlation coefficient = 0.85, P<0.001), excluding either CONUT or PNI from the multivariable model would render the other variable statistically significant in predicting mortality.

Of the variables that were significant in univariable analysis (excluding 3 frailty tools), sodium, recurrent falls and PNI were significant predictors of mortality in a multivariable model including malnutrition tools (Table 5.4b).

Addition of malnutrition and frailty tools to the base models both increased model performance for mortality prediction (Table 5.5). Amongst the malnutrition tools: PNI; and amongst the frailty tools: CFS, increased model performance most compared to the base model.

Table 5.5: Addition of frailty and malnutrition tools and its impact on performance of base model in predicting all-cause mortality.

Model	**Harrell's C-statistic**	**P** (compared to base model)
Malnutrition base model*	0.74	-
+ CONUT score	0.80	<0.001
+ GNRI	0.78	0.001
+ PNI	0.81	<0.001
Frailty base model**	0.68	-
+ AFN	0.74	0.009
+ CFS	0.81	<0.001
+ DFI	0.76	0.004

CONUT= controlling nutritional index, GNRI = Geriatric Nutritional Risk Index, PNI = Prognostic Nutritional Index, AFN = Acute Frailty Network Frailty criteria, CFS = Clinical Frailty Scale, DFI = Derby Frailty Index.

*Variables included in the malnutrition base model: age, sex, Hb, AF, log[NT-ProBNP], creatinine, sodium, recurrent falls and IHD.

** Variables included in the frailty base model: sex, Hb, AF, log [NT-proBNP, creatinine, sodium and IHD. Age and recurrent falls were excluded as they are part of the DFI and AFN.

Of the variables that were significant in univariable analysis, only PNI and CFS were significant predictors of mortality in the final survival model (Table 5.6). Adding both CFS and PNI to the base model including sex, Hb, AF, log [NT-proBNP], creatinine, sodium, recurrent falls and IHD, had a Harrell's C-statistic of 0.84.

Table 5.6: Multivariable analysis of CFS and PNI predicting all-cause mortality.

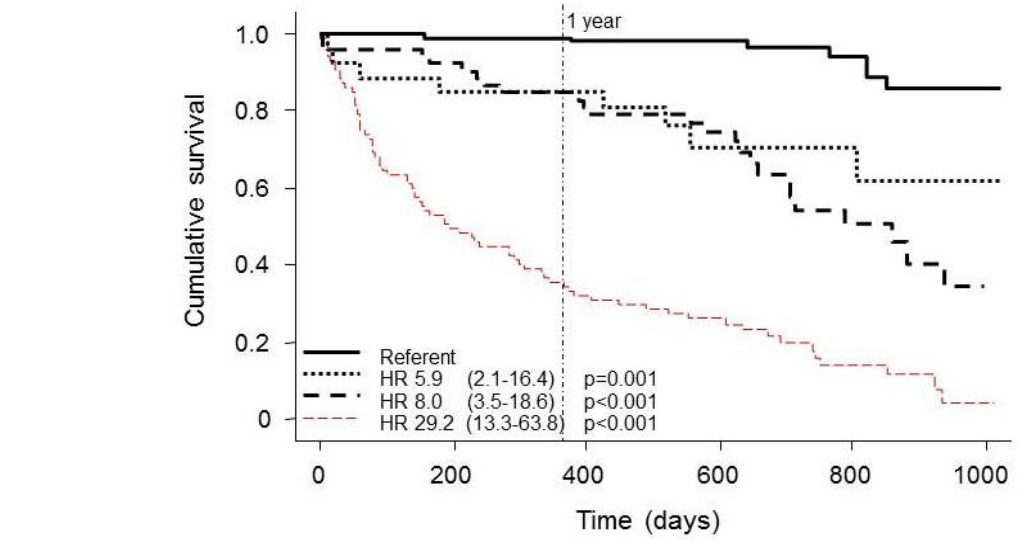
Worse outcome per unitary increase	**HR (95%CI)**	**Wald χ^2**	**P**
Age (years)	0.99 (0.97-1.02)	0.01	0.9
Sex (male vs female)	0.82 (0.54-1.24)	0.9	0.4
Hb (g/dL)	1.02 (0.91-1.13)	0.1	0.8
AF (Y vs N)	1.10 (0.73-1.67)	0.2	0.7
Log [NT-ProBNP]	1.45 (0.88-2.40)	2.2	0.1
Creatinine (per 10 µmol/L)	1.03 (1.00-1.05)	4.7	0.03
Sodium (mmol/L)	0.97 (0.94-1.01)	2.5	0.1
Recurrent Falls (Y vs N)	1.53 (0.94-2.50)	2.9	0.09
IHD (Y vs N)	1.06 (0.70-1.60)	0.1	0.8
CFS (increasing score)	1.55 (1.35-1.77)	39.1	<0.001
PNI (decreasing score)	1.09 (1.06-1.12)	28.0	<0.001

C-statistic = 0.84.

HR = hazard ratio, CI= confidence interval, χ^2= chi-square, IHD = ischaemic heart disease, PNI = Prognostic Nutritional Index, CFS = Clinical Frailty Scale, Hb = Haemoglobin, NT-proBNP = N-terminal Pro Brain Natriuretic Peptide, AF= atrial fibrillation, Y = yes, N=no.

Patients who were frail and malnourished had an almost 30 times greater mortality risk than those who were neither frail nor malnourished (Figure 5.4). Mortality at 1 year was 65% for those who were frail and malnourished; 15% for those who were either frail or malnourished and only 1% for those who were neither frail nor malnourished.

Figure 5.4: Kaplan Meier curves illustrating the relation between combined groups of frailty and malnutrition and all-cause mortality.



Not malnourished & not frail	100	99	98	74	39	6
Malnourished & not frail	26	22	22	10	8	1
Not malnourished & frail	52	48	41	29	14	0
Malnourished & frail	86	43	28	18	6	1

5.5 Discussion

This study showed that frailty and malnutrition are both very common amongst patients admitted to hospital with HF. The prevalence of frailty and malnutrition in this cohort was around 50% and 45% respectively, comparable to findings from other studies (36-51% for frailty (156) and 75-90% for malnutrition (118) in patients admitted with HF). Direct comparison of the frailty and malnutrition tools demonstrated substantial overlap between patients identified as either frail or malnourished by each tool, however, the overlap was not absolute. Although there seemed to be correlation between increasing frailty and worsening malnutrition, the relation was weak: only around 20% of the variation was due to variation in the other. This finding suggests that frailty and malnutrition, despite having overlapping features, are distinct entities.

Another significant finding is that both frailty and malnutrition were strongly related to outcome in patients hospitalised with HF. In the final multivariate survival model, only CFS and PNI were significant predictors of mortality. These frailty and malnutrition tools

eliminated all other variables as potential predictors of outcome, presumably because they include many aspects of other potential clinical variables in a composite score.

The pathophysiology of malnutrition and cachexia in HF is complicated (91). Patients with HF have a higher basal metabolic rate due to increased work of breathing. Gut oedema and hepatic congestion may also contribute to nausea, early satiety and reduced food absorption. Furthermore, HF is a chronic inflammatory state which induces metabolic disturbances. Impaired cardiac pump function and subsequent hypoperfusion of peripheral tissues leads to a systemic response characterised by inflammatory and neurohormonal activation. These responses results in insulin resistance and anabolic-catabolic imbalance (91).

The CONUT score is calculated from variables reflecting both protein and lipid metabolism, as well as immune function. PNI is similar to the CONUT score but does not include cholesterol, which might be more appropriate in patients with HF as a significant proportion (54% in our cohort) take statins which cause lower cholesterol levels irrespective of nutritional status. GNRI was the weakest predictor of mortality, perhaps because GNRI includes weight loss. Weight loss is unreliable marker of nutritional status in patients with HF, especially in those with decompensated HF, because of the influence of oedema and the use of diuretics. Assessment of body composition rather than direct weight measurements might be more appropriate.

Amongst the frailty tools, CFS had the strongest prognostic value. CFS is a more complex tool giving a scored result, whereas AFN and DFI are simple “yes/no” screening tools. CFS is not without its limitations - there is an element of subjectivity, which introduces bias.

The management of both frailty and malnutrition is a medical challenge. Exercise therapy, nutritional supplementation and multidisciplinary management may be beneficial (158-161). Consensus definitions for malnutrition and frailty are needed so that comparable intervention trials can be designed to study potential treatment for these conditions.

5.6 Study limitations

Firstly, this is a single-centre study conducted in the UK with limited sample size; external validation of our results from centres in other countries with different healthcare and social systems is needed. Secondly, I have only studied 6 of the large number of screening tools proposed to assess frailty and malnutrition. Thirdly, I have not compared the prognostic value of simple malnutrition tools with more complex multi-dimensional tools (136-138). Similarly, I have only looked at frailty screening tools; the role of more comprehensive assessment tools has not been studied (44, 72, 80).

5.7 Conclusion

Frailty and malnutrition, as determined by simple screening tools, are very common in patients hospitalised for HF and are powerful predictors of mortality. CFS and PNI might be useful when assessing patients with AHF to identify individuals at high risk of mortality. Further studies are needed to establish consensus measures of frailty and malnutrition in different cohorts of patients with HF.

Chapter 6 Prevalence, Clinical Associations and Prognostic Significance of Malnutrition in Patients with Chronic Heart Failure

6.1 Chapter summary

Background: Malnutrition may be common in patients with CHF and associated with adverse outcomes, but few data exist.

Objectives: To study the prevalence, clinical associations and prognostic significance of malnutrition in patients with CHF.

Methods: I evaluated malnutrition using the COntroling NUTritional Status (CONUT) score, Geriatric nutritional risk index (GNRI) and Prognostic nutritional index (PNI), in consecutive patients referred with suspected HF to our clinic.

Results: Of 4,021 patients enrolled, HF was confirmed in 3386 (61% men, median age 75 (IQR: 67-81) years, median NT-proBNP 1,103 (IQR: 415-2631) ng/L). LVEF was <40% in 35%. According to the CONUT score (>4), GNRI (≤91) and PNI (≤38), 10.0%, 6.7% and 7.5% patients were moderately to severely malnourished respectively; 57% were at least mildly malnourished by at least one tool. Worsening malnutrition was related to older age, lower BMI, worse symptoms and renal function, AF, anaemia and reduced mobility.

During a median follow-up of 1573 days (IQR: 702-2799 days), 1723 (51%) patients died. For patients with moderate to severe malnutrition, 1-year mortality was 28% for CONUT, 41% for GNRI and 36% for PNI, compared to 9% for those with mild malnutrition or normal nutritional status.

A model including age, urea and log [NT-proBNP], predicted one year survival (Harrell's C-statistic = 0.719) and was slightly improved by adding nutritional indices (up to 0.724; P<0.001) but not BMI.

Conclusion: Malnutrition is common in patients with CHF and is strongly related to increased mortality.

6.2 Introduction

Although often ignored, malnutrition appears to be common in patients with CHF and associated with a high mortality (91, 157). According to a systematic review on malnutrition evaluation in patients with HF, the prevalence of malnutrition has been reported to be as high as 62% in some CHF populations (118). Malnutrition determined by any tool, has also been shown to be an independent predictor of worsening HF and/or mortality (118).

Severe HF may lead to loss of appetite, malabsorption and hypercatabolism, predisposing to malnutrition (91). Malnutrition may also drive disease progression as part of a vicious cycle associated with cytokine activation, autonomic dysfunction and cachexia (162).

Screening patients with CHF for malnutrition might identify patients at high risk of adverse outcomes who might benefit from tailored treatments to prevent deterioration in HF and improve prognosis (91). There are many malnutrition tools available but no consensus on which to use for patients with CHF (118). Amongst malnutrition screening tools, the COntrolling NUTritional Status index **(**CONUT), the prognostic nutritional index (PNI) and the geriatric nutritional risk index (GNRI) have been studied in HF (118). However, the studies conducted so far have been small (N = 50-538) and may not have been epidemiologically representative of the general population with CHF (118).

In Chapter 5, I have explored the role of malnutrition in patients admitted with HF. In this chapter, I will investigate the prevalence, clinical associations and prognostic significance of malnutrition using 3 simple malnutrition tools in a large, well-characterised cohort of ambulatory patients with CHF.

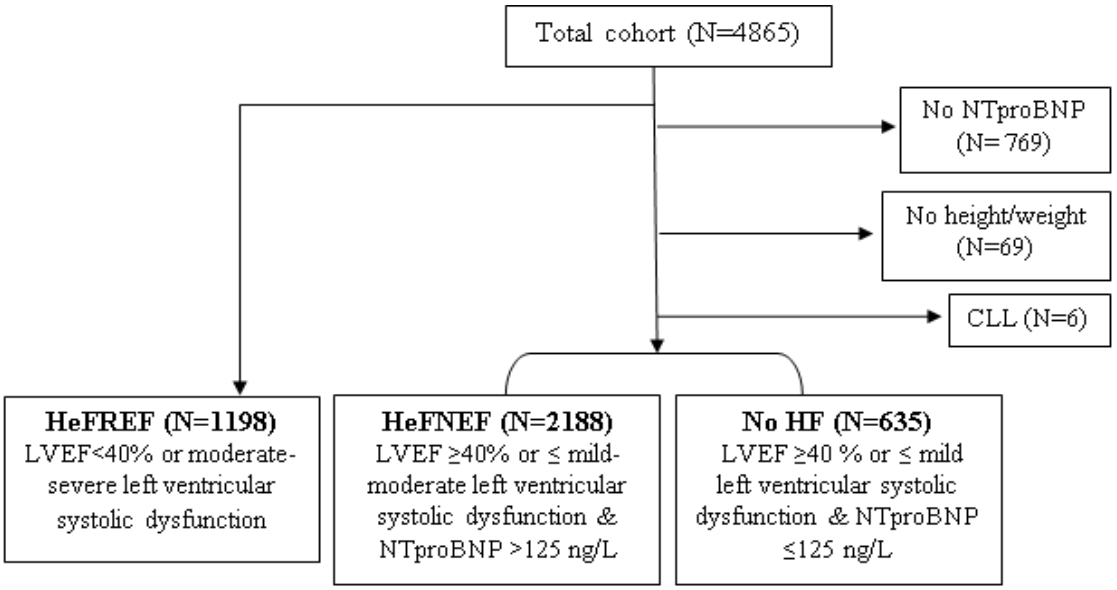
6.3 Methods

6.3.1 Study population

I studied retrospectively, consecutive patients referred to our community HF clinic at Castle Hill Hospital, Hull, UK, between 2000 and 2016 with suspected HF. The

recruitment process is shown in Figure 6.1. Patients with recorded measurements of height, weight and NT-proBNP at baseline visit were included. I excluded 6 patients with a diagnosis of chronic lymphocytic leukaemia as they have elevated levels of serum lymphocyte count which directly impacts on the calculation of CONUT score and PNI. A detailed description of the study population can be found in Chapter 4.

Figure 6.5: Recruitment of patients.



CLL = chronic lymphocytic leukaemia, HeFREF = heart failure with reduced ejection fraction, HeFNEF= heart failure with normal ejection fraction, LVEF= left ventricular ejection fraction, NT-proBNP = N-terminal Pro Brain Natriuretic Peptide.

Patients with an LVEF ≥40% and NT-proBNP ≤125ng/L were considered not to have HF. Patients with HF were phenotyped as HeFREF or HeFNEF according to the HF definitions detailed in Chapter 4.

In order to study the relation between malnutrition and NT-proBNP / BMI, I further stratified HF patients into 5 NT-proBNP (ng/L) categories (≤400, 401-1000, 1001-2000, 2001-4000 and >4000) and 5 BMI (kg/m^2) categories (underweight: BMI<18.5, normal: BMI = 18.5-24.9, overweight: BMI = 25.0-29.9, obese: BMI = 30-39.9 and morbidly obese: BMI ≥40) (163).

6.3.2 Malnutrition evaluation

I evaluated malnutrition in patients using the following 3 simple tools:

1) COntroling NUTritional Status (CONUT) score
2) Geriatric nutritional risk index (GNRI)
3) Prognostic nutritional index (PNI).

A description of the malnutrition evaluation process can be found in the 'malnutrition evaluation' section in Chapter 4.

6.3.3 End point and follow up

I followed the patients until 19th July 2016 and the primary end point was all-cause mortality.

6.3.4 Statistical analysis

Routine statistical analyses have been detailed in Chapter 4. Firstly, I studied the prevalence of malnutrition, initially in the entire cohort, then in different subgroups of patients with CHF. Then, I used Venn diagrams to illustrate the relationship amongst the malnutrition tools. Thirdly, I explored the clinical associations of malnutrition. Finally, I studied the relationship between malnutrition tools and mortality using Cox proportional hazards regression.

The 'one-stop prognostic model' approach, although still favoured by many, fell into disrepute more than 30 years ago (164, 165). Cross-validation, using an intuitive approach, brings both consistency and variability to prognostic model development (166). Therefore, I used k-fold cross-validation (k=25 here) to generate 25 prognostic models. Crossfold-validation splits the data randomly into 25 partitions. For each partition, the specified Cox regression model was fitted using the other *k*-1 (i.e. 24) groups, and the results were used to predict the dependent variable in the unused group.

I included all the variables listed in Table 6.1a in the Cox models except: albumin, cholesterol and lymphocyte count which are included in the CONUT score and PNI; and weight, height and BMI which are included in the GNRI.

An arbitrary level of 5% statistical significance (two-tailed) was assumed for a covariate to be included in the model. The frequency of inclusion in all 25 prognostic models was calculated. I used the variables with an arbitrary inclusion frequency of ≥18 (in at least 70% of the 25 prognostic models) to form a malnutrition base model. Then, I addded each of the malnutrition tools in turn to the base model and used Harrell's C-statistic and log-likelihood ratio (LLR) to evaluate model discrimination in survival analysis.

6.4 Results

6.4.1 Baseline characteristics

Baseline characteristics of patients with CHF vs those without HF are shown in Table 6.1a. Baseline characteristics of patients with HeFREF vs those with HeFNEF are shown in Table 6.1b.

Of the 4021 patients enrolled, 3386 had CHF: 1198 (35%) patients had HeFREF, 2188 (65%) patients had HeFNEF and 635 did not have HF (Tables 6.1a-b). Most patients with CHF were men (61%) and median age was 75 (IQR: 67-81) years. Median NT-proBNP was 1,103 (IQR: 415-2,631) ng/L). A third of patients (30%) had severe symptoms (NYHA class III/IV). The most common co-morbidity was IHD (48% of cases), and 36% were obese (BMI ≥ 30 kg/m^2).

Table 6.1a. Baseline characteristics of patients with CHF vs those without HF.

	No HF N=635	**CHF** N=3386	Missing	**P**
Demographics				
Sex (male), n (%)	342 (54)	2063 (61)	0	0.001
Age (years)	67 (59-73)	75 (67-81)	0	<0.001
BP systolic (mmHg)	144 (129-159)	139 (121-157)	5	<0.001
BP diastolic (mmHg)	82 (74-91)	78 (69-88)	5	<0.001
HR (bpm)	72 (64-82)	72 (62-85)	13	0.08
Height (m)	1.67 (1.60-1.74)	1.67 (1.59-1.74)	0	0.06
Weight (kg)	85 (73-97)	78 (67-91)	0	<0.001
BMI (kg/m^2)	30 (27-34)	28 (25-32)	0	<0.001
Cardiac rhythm, n (%)			0	<0.001
- AF	0	973 (29)		
- SR	628 (99)	2214 (65)		
- Unknown	6 (1)	199 (6)		
NYHA, n (%)			0	<0.001
- I	302 (48)	711 (21)		
- II	244 (38)	1660 (49)		
- III	83 (13)	952 (28)		
- IV	5 (1)	63 (2)		
Co-morbidities				
HTN, n (%)	252 (40)	1245 (37)	0	0.16
IHD, n (%)	153 (24)	1606 (48)	0	<0.001
CVD, n (%)	20 (3)	237 (7)	0	<0.001
PVD, n (%)	13 (2)	146 (4)	0	0.007
Diabetes Mellitus, n (%)	169 (27)	819 (26)	0	0.19
COPD, n (%)	63 (10)	325 (10)	0	0.80
Malignancy, n (%)	33 (5)	302 (9)	0	0.002
Reduced mobility, n (%)	210 (33)	1823 (63)	0	<0.001

Table 6.7a (continued): Baseline characteristics of patients with CHF vs those without HF.

	No HF N=635	**CHF** N=3386	Missing	**P**
Medications				
ACEi/ARB, n (%)	292 (47)	2315 (69)	0	<0.001
BB, n (%)	169 (27)	1876 (56)	0	<0.001
MRA, n (%)	23 (4)	631 (19)	5	<0.001
Loop diuretics, n (%)	184 (29)	2147 (64)	5	<0.001
Digoxin, n (%)	10 (2)	587 (18)	13	<0.001
Statin, n (%)	299 (48)	1726 (52)	0	0.09
Blood tests				
NT-ProBNP (ng/L)	64 (38-92)	1103 (415-2631)	0	NA
Hb (g/dL)	14.0 (13.2-15.0)	13.3 (12.1-14.4)	0	<0.001
Urea (mmol/L)	5.2 (4.2-6.3)	6.8 (5.2-9.3)	0	<0.001
Creatinine (µmol/L)	82 (71-96)	100 (81-126)	0	<0.001
Sodium (mmol/L)	139 (137-141)	139 (137-140)	0	<0.001
Potassium (mmol/L)	4.3 (4.0-4.5)	4.3 (4.0-4.6)	0	<0.001
Albumin (g/L)	40 (37-41)	38 (35-40)	0	<0.001
Cholesterol (mmol/L)	4.9 (4.1-5.8)	4.5 (3.7-5.4)	0	<0.001
Lymphocyte ($x10^9$/L)	1.9 (1.6-2.3)	1.6 (1.2-2.1)	0	<0.001

Table 6.1b: Baseline characteristics of HeFREF vs HeFNEF patients.

	HeFREF N=1198	**HeFNEF** N=2188	**P**
Demographics			
Sex (male), n (%)	895 (75)	1168 (53)	<0.001
Age (years)	73 (64-79)	76 (70-82)	<0.001
BP systolic (mmHg)	128 (113-143)	145 (127-162)	<0.001
BP diastolic (mmHg)	76 (67-87)	78 (70-89)	<0.001
HR (bpm)	75 (64-88)	72 (62-83)	<0.001
Height (m)	1.69 (1.62-1.76)	1.65 (1.58-1.73)	<0.001
Weight (kg)	78 (66-90)	79 (67-92)	0.01
BMI (kg/m^2)	27 (24-31)	29 (25-33)	<0.001
Cardiac rhythm, n (%)			<0.001
- AF	278 (23)	695 (32)	
- SR	833 (70)	1382 (63)	
- Unknown	87 (7)	112 (5)	
NYHA, n (%)			<0.001
- I	165 (14)	547 (25)	
- II	598 (50)	1062 (49)	
- III	401 (33)	551 (25)	
- IV	34 (3)	29 (1)	
Co-morbidities			
HTN, n (%)	367 (31)	878 (40)	<0.001
IHD, n (%)	768 (64)	838 (38)	<0.001
CVD, n (%)	104 (9)	133 (6)	0.004
PVD, n (%)	72 (6)	74 (3)	<0.001
Diabetes Mellitus, n (%)	274 (23)	546 (25)	0.18
COPD, n (%)	113 (9)	212 (10)	0.81
Malignancy, n (%)	94 (8)	208 (10)	0.11
Reduced mobility, n (%)	620 (52)	1203 (55)	0.07

Table 6.1b (continued): Baseline characteristics of HeFREF vs HeFNEF patients.

	HeFREF N=1198	**HeFNEF** N=2188	**P**
Medications			
ACEi/ARB, n (%)	966 (81)	1349 (62)	<0.001
BB, n (%)	758 (64)	1119 (52)	<0.001
MRA, n (%)	369 (31)	262 (12)	<0.001
Loop diuretics, n (%)	904 (76)	1243 (57)	<0.001
Digoxin, n (%)	203 (17)	384 (18)	0.65
Statin, n (%)	634 (53)	1093 (51)	0.10
Blood tests			
NT-ProBNP (ng/L)	1974 (831-4534)	812 (309-1845)	<0.001
Hb (g/dL)	13.5 (12.3-14.7)	13.2 (12.0-14.3)	<0.001
Urea (mmol/L)	7.1 (5.4-9.9)	6.6 (5.1-9.1)	<0.001
Creatinine (µmol/L)	105 (88-133)	95 (79-121)	<0.001
Sodium (mmol/L)	139 (136-140)	139 (137-140)	0.009
Potassium (mmol/L)	4.4 (4.1-4.7)	4.3 (4.0-4.6)	0.003
Albumin (g/L)	38 (35-40)	38 (35-40)	0.09
Cholesterol (mmol/L)	4.4 (3.7-5.3)	4.5 (3.7-5.4)	0.08
Lymphocyte ($x10^9$/L)	1.6 (1.2-2.1)	1.7 (1.3-2.1)	0.46

ACEi = Angiotensin-converting enzyme inhibitor, AF= atrial fibrillation, SR= sinus rhythm, ARB = Angiotensin receptor blocker, BB= betablocker, BMI= body mass index, BP= blood pressure, COPD = chronic obstructive pulmonary disease, CVD = cerebrovascular disease, PVD = peripheral vascular disease, Hb = Haemoglobin, HeFREF = heart failure with reduced ejection fraction, HeFNEF = heart failure with normal ejection fraction, HR= heart rate, HTN= hypertension, IHD = ischaemic heart disease, MRA = Mineralocorticoids receptor antagonists, NYHA = New York Heart Association Class, NT-proBNP = N-terminal Pro Brain Natriuretic Peptide.

6.4.2 Prevalence and clinical associations of malnutrition

The prevalence of malnutrition is much higher in patients with CHF compared to those without HF (Table 6.2). According to the CONUT score and GNRI, 1486 (44%) and 316 (9%) patients with CHF had mild malnutrition respectively. According to the CONUT score, GNRI and PNI, 339 (10%), 228 (7%) and 255 (8%) patients had moderate to severe malnutrition respectively.

Table 6.2: Prevalence of malnutrition in the entire cohort.

		No HF N=635	**CHF**		**P** CHF vs no HF	**P** HeFREF vs HeFNEF
			HeFREF N=1198	HeFNEF N=2188		
CONUT	Normal (0-1)	450 (71)	552 (46)	1010 (46)	<0.001	0.09
	Mild (2-4)	181 (29)	507 (42)	979 (45)		
	Moderate (5-8)	3 (<1)	129 (11)	190 (9)		
	Severe (9-12)	0	10 (1)	10 (<1)		
GNRI	Normal (>98)	614 (96)	969 (81)	1874 (86)	<0.001	0.003
	Mild (92-98)	16 (3)	133 (11)	183 (8)		
	Moderate (82-91)	4 (1)	71 (6)	106 (5)		
	Severe (<82)	0	25 (2)	26 (1)		
PNI	Normal (>38)	633 (100)	1101 (92)	2023 (93)	<0.001	0.65
	Moderate (35-38)	1 (0)	53 (4)	86 (4)		
	Severe (<35)	0	44 (4)	72 (3)		

HeFREF = heart failure with reduced ejection fraction, HeFNEF = heart failure with normal ejection fraction, CONUT = Controlling nutritional status, GNRI = Geriatric nutritional risk index, PNI = Prognostic nutritional Index.

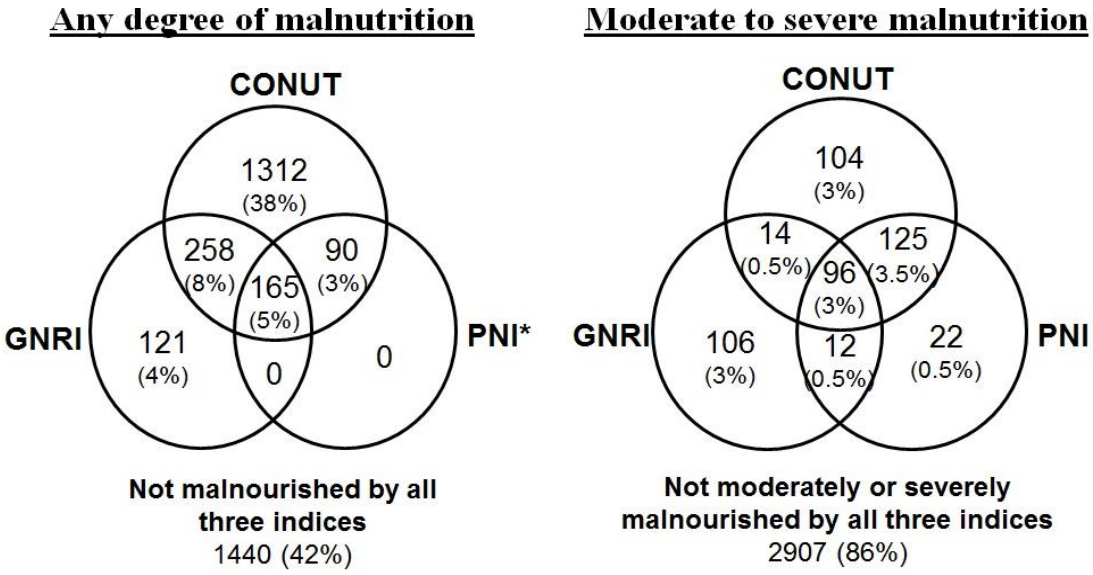
Although malnutrition tools correlated with each other (Table 6.3), only 5% were classified as malnourished (any degree of malnutrition) by all 3 tools, and only 42% were *not* malnourished by any (Figure 6.2). Because PNI has no "mild" category for malnutrition, the overlap amongst patients identified as moderately to severely malnourished by the different tools is more striking.

Table 6.3: Correlation coefficients for malnutrition tools.

Tools	CONUT	GNRI
GNRI	-0.36	
PNI	-0.72	0.42

All P<0.001.
CONUT = Controlling nutritional status, GNRI = Geriatric nutritional risk index, PNI = Prognostic nutritional Index.

Figure 6.6: Prevalence of malnutrition by CONUT, GNRI and PNI.



*PNI only classifies patients as normal, moderately or severely malnourished; there is no mild malnutrition category.
CONUT = Controlling nutritional status, GNRI = Geriatric nutritional risk index, PNI = Prognostic nutritional Index.

Tables 6.4a-c show the baseline characteristics of patients with CHF by malnutrition categories according to the CONUT score (Table 6.4a), GNRI (Table 6.4b) and PNI (Table 6.4c). Compared to those with normal nutritional status, patients with malnutrition measured by any of the three malnutrition tools were older, more likely to be men, had lower BMI, worse symptoms and renal function; they were also more likely to have AF, anaemia and reduced mobility (Tables 6.4a-c).

Table 6.4a: Baseline characteristics of CHF patients by CONUT categories.

	Normal	Malnutrition			P
	0-1	Mild	Moderate	Severe	
	N= 1561	2-4 N=1486	5-8 N=319	9-12 N=20	
Demographics					
Sex (male), n (%)	851 (55)	964 (65)	233 (73)	15 (75)	<0.001
Age (years)	73 (65-80)	75 (69-81)	77 (71-82)	78 (69-83)	<0.001
BP systolic (mmHg)	140 (124-160)	139 (121-156)	126 (110-149)	105 (94-119)	<0.001
BP diastolic (mmHg)	80 (71-90)	77 (68-87)	72 (63-81)	60 (56-70)	<0.001
HR (bpm)	72 (63-84)	71 (62-84)	78 (64-89)	78 (70-88)	0.001
Height (m)	1.66 (1.58-1.74)	1.68 (1.60-1.74)	1.68 (1.61-1.75)	1.70 (1.61-1.76)	0.01
Weight (kg)	79 (68-91)	79 (67-91)	75 (64-87)	70 (65-86)	0.04
BMI (kg/m^2)	29 (25-32)	28 (25-32)	26 (24-30)	25 (22-30)	<0.001
Cardiac rhythm, n (%)					<0.001
- AF	380 (24)	465 (31)	119 (37)	9 (45)	
- SR	1103 (71)	925 (62)	178 (56)	8 (40)	
- Unknown	78 (5)	96 (7)	22 (7)	3 (15)	
NYHA, n (%)					<0.001
- I	388 (25)	291 (20)	31 (10)	1 (5)	
- II	817 (52)	705 (47)	132 (41)	6 (30)	
- III	336 (22)	463 (31)	142 (45)	11 (55)	
- IV	20 (1)	27 (2)	14 (4)	2 (10)	
HeFREF, n (%)	552 (35)	507 (34)	129 (41)	10 (50)	0.02
Co-morbidities					
HTN, n (%)	593 (38)	549 (37)	97 (30)	6 (30)	0.07
IHD, n (%)	666 (43)	775 (52)	154 (48)	11 (55)	<0.001
CVD, n (%)	91 (6)	107 (7)	36 (11)	3 (15)	0.002
PVD, n (%)	54 (4)	70 (5)	22 (7)	0	0.03
Diabetes Mellitus, n (%)	310 (21)	411 (29)	96 (32)	2 (11)	<0.001
COPD, n (%)	136 (9)	150 (10)	37 (12)	2 (10)	0.35
Malignancy, n (%)	131 (8)	133 (9)	32 (10)	6 (30)	0.008
Reduced mobility, n (%)	739 (56)	859 (67)	210 (76)	15 (94)	<0.001

Table 6.4a (continued): Baseline characteristics of CHF patients by CONUT categories.

	Normal	Malnutrition			P
	0-1	Mild	Moderate	Severe	
	N= 1561	2-4 N=1486	5-8 N=319	9-12 N=20	
Medications					
ACEi/ARB, n (%)	1070 (69)	1033 (70)	203 (64)	9 (45)	0.02
BB, n (%)	858 (55)	839 (57)	169 (54)	10 (50)	0.57
MRA, n (%)	266 (17)	309 (21)	50 (16)	6 (30)	0.01
Loop diuretics, n (%)	919 (59)	977 (67)	234 (74)	17 (85)	<0.001
Digoxin, n (%)	248 (16)	253 (17)	80 (25)	6 (30)	<0.001
Statin, n (%)	685 (44)	850 (58)	180 (57)	11 (55)	<0.001
Blood tests					
NT-ProBNP (ng/L)	790 (305-1772)	1291 (498-2935)	3873 (1516-7693)	6071 (2223-20466)	<0.001
Hb (g/dL)	13.7 (12.7-14.8)	13.1 (12.0-14.2)	11.8 (10.6-12.9)	10.8 (9.6-12.9)	<0.001
Urea (mmol/L)	6.4 (5.0-8.6)	7.0 (5.3-9.5)	8.5 (6.1-12.5)	10.6 (8.2-12.5)	<0.001
Creatinine (µmol/L)	94 (79-115)	103 (83-129)	117 (91-162)	134 (97-177)	<0.001
Sodium (mmol/L)	139 (137-141)	139 (136-140)	138 (135-140)	135 (133-138)	<0.001
Potassium (mmol/L)	4.3 (4.1-4.7)	4.3 (4.0-4.6)	4.3 (4.0-4.7)	4.1 (3.9-4.6)	0.05
Albumin (g/L)	39 (37-41)	37 (35-39)	32 (29-34)	24 (22-28)	<0.001
Cholesterol (mmol/L)	5.1 (4.4-5.9)	4.0 (3.4-4.8)	3.5 (2.9-4.2)	2.9 (2.5-3.3)	<0.001
Lymphocyte ($x10^9$/L)	1.9 (1.7-2.3)	1.4 (1.1-1.8)	1.1 (0.8-1.4)	0.6 (0.5-0.9)	<0.001

Table 6.4b: Baseline characteristics of CHF patients by GNRI categories.

	Normal	Malnutrition			P
	>98	Mild	Moderate	Severe	
	N= 2842	92-98	82-91	<82	
		N=316	N=177	N=51	
Demographics					
Sex (male), n (%)	1757 (62)	182 (58)	97 (55)	27 (53)	0.09
Age (years)	74 (67-80)	78 (72-84)	78 (72-83)	79 (74-84)	<0.001
BP systolic (mmHg)	140 (123-158)	133 (116-151)	123 (109-148)	118 (103-136)	<0.001
BP diastolic (mmHg)	79 (70-89)	74 (65-84)	70 (60-79)	68 (58-76)	<0.001
HR (bpm)	72 (62-84)	77 (66-88)	77 (64-90)	82 (74-90)	<0.001
Height (m)	1.67 (1.59-1.75)	1.66 (1.58-1.72)	1.65 (1.58-1.72)	1.65 (1.58-1.76)	0.006
Weight (kg)	82 (71-94)	63 (56-69)	57 (49-66)	55 (43-61)	<0.001
BMI (kg/m^2)	29 (26-33)	23 (21-24)	21 (19-23)	19 (17-21)	<0.001
Cardiac rhythm, n (%)					0.11
- AF	803 (28)	100 (32)	52 (30)	18 (35)	
- SR	1872 (66)	193 (61)	121 (68)	28 (55)	
- Unknown	167 (6)	23 (7)	4 (2)	5 (10)	
NYHA, n (%)					<0.001
- I	616 (22)	64 (20)	26 (15)	5 (10)	
- II	1418 (50)	144 (46)	82 (46)	16 (31)	
- III	762 (27)	101 (32)	61 (34)	28 (55)	
- IV	46 (1)	7 (2)	8 (5)	2 (4)	
HeFREF, n (%)	969 (34)	133 (42)	71 (40)	25 (49)	0.001
Co-morbidities					
HTN, n (%)	1091 (38)	101 (32)	46 (26)	7 (14)	<0.001
IHD, n (%)	1364 (48)	141 (45)	76 (43)	25 (49)	0.42
CVD, n (%)	188 (7)	32 (10)	12 (7)	5 (10)	0.11
PVD, n (%)	115 (4)	17 (5)	13 (7)	1 (2)	0.11
Diabetes Mellitus, n (%)	745 (28)	45 (15)	24 (15)	5 (10)	<0.001
COPD, n (%)	240 (8)	39 (12)	38 (22)	8 (16)	<0.001
Malignancy, n (%)	245 (9)	29 (9)	18 (10)	10 (20)	0.05
Reduced mobility, n (%)	1507 (62)	170 (62)	111 (73)	35 (83)	0.01

Table 6.4b (continued): Baseline characteristics of CHF patients by GNRI categories.

	Normal	Malnutrition			P
	>98	Mild	Moderate	Severe	
	N= 2842	92-98	82-91	<82	
		N=316	N=177	N=51	
Medications					
ACEi/ARB, n (%)	1976 (70)	194 (62)	119 (68)	26 (54)	0.003
BB, n (%)	1614 (57)	161 (51)	83 (47)	18 (38)	0.001
MRA, n (%)	536 (19)	56 (18)	31 (18)	8 (17)	0.90
Loop diuretics, n (%)	1764 (63)	213 (68)	129 (73)	41 (85)	<0.001
Digoxin, n (%)	442 (16)	88 (28)	42 (24)	15 (31)	<0.001
Statin, n (%)	1529 (54)	121 (39)	56 (34)	17 (35)	<0.001
Blood tests					
NT-ProBNP (ng/L)	930 (364-2167)	2518 (1104-4757)	3016 (1266-7428)	4854 (1787-9447)	<0.001
Hb (g/dL)	13.5 (12.3-14.5)	12.6 (11.4-13.8)	12.5 (11.1-13.5)	12.0 (10.4-13.4)	<0.001
Urea (mmol/L)	6.7 (5.2-9.2)	7.1 (5.4-10.5)	7.5 (5.6-10.5)	8.4 (5.5-11.3)	0.003
Creatinine (µmol/L)	100 (82-125)	100 (79-131)	101 (77-131)	107 (79-137)	0.87
Sodium (mmol/L)	139 (137-141)	138 (136-140)	137 (134-139)	136 (134-139)	<0.001
Potassium (mmol/L)	4.3 (4.1-4.7)	4.4 (4.1-4.6)	4.3 (4.0-4.7)	4.3 (3.8-4.6)	0.37
Albumin (g/L)	38 (36-40)	35 (33-37)	32 (30-35)	29 (24-30)	<0.001
Cholesterol (mmol/L)	4.5 (3.7-5.4)	4.5 (3.6-5.4)	4.4 (3.6-5.2)	4.3 (3.6-5.1)	0.04
Lymphocyte ($x10^9$/L)	1.7 (1.3-2.1)	1.4 (1.1-1.8)	1.4 (1.0-1.7)	1.2 (0.9-1.6)	<0.001

Table 6.4c: Baseline characteristics of CHF patients by PNI categories.

	Normal	**Malnutrition**		**P**
	>38	**Moderate**	**Severe**	
	N= 3131	35-38	<35	
		N=139	N=116	
Demographics				
Sex (male), n (%)	1888 (60)	95 (68)	80 (69)	0.03
Age (years)	75 (67-81)	75 (68-82)	78 (72-82)	0.004
BP systolic (mmHg)	139 (122-158)	124 (111-146)	125 (105-152)	<0.001
BP diastolic (mmHg)	78 (69-89)	73 (63-81)	70 (59-81)	<0.001
HR (bpm)	72 (62-84)	77 (69-90)	80 (68-92)	<0.001
Height (m)	1.67 (1.59-1.74)	1.68 (1.62-1.73)	1.68 (1.61-1.77)	0.10
Weight (kg)	79 (67-91)	74 (65-86)	72 (61-88)	0.002
BMI (kg/m^2)	28 (25-32)	26 (24-29)	26 (22-30)	<0.001
Cardiac rhythm, n (%)				0.001
- AF	874 (28)	51 (37)	48 (41)	
- SR	2078 (66)	76 (55)	60 (52)	
- Unknown	179 (6)	12 (8)	8 (7)	
NYHA, n (%)				<0.001
- I	692 (22)	11 (8)	8 (7)	
- II	1563 (50)	59 (42)	38 (33)	
- III	829 (26)	58 (42)	65 (56)	
- IV	47 (2)	11 (8)	5 (4)	
HeFREF, n (%)	1101 (35)	53 (38)	44 (38)	0.54
Co-morbidities				
HTN, n (%)	1166 (37)	42 (30)	37 (32)	0.13
IHD, n (%)	1499 (48)	55 (40)	52 (45)	0.14
CVD, n (%)	207 (7)	16 (12)	14 (12)	0.008
PVD, n (%)	130 (4)	10 (7)	6 (5)	0.20
Diabetes Mellitus, n (%)	755 (25)	34 (27)	30 (28)	0.91
COPD, n (%)	287 (9)	27 (19)	11 (10)	<0.001
Malignancy, n (%)	269 (9)	19 (14)	14 (12)	0.06
Reduced mobility, n (%)	1646 (62)	101 (82)	76 (80)	<0.001

Table 6.4c (continued): Baseline characteristics of CHF patients by PNI categories.

	Normal	Malnutrition		P
	>38	Moderate	Severe	
	N= 3131	35-38	<35	
		N=139	N=116	
Medications				
ACEi/ARB, n (%)	2173 (70)	79 (57)	63 (56)	<0.001
BB, n (%)	1761 (57)	65 (47)	50 (45)	0.004
MRA, n (%)	594 (19)	19 (14)	18 (16)	0.22
Loop diuretics, n (%)	1957 (63)	101 (73)	89 (80)	<0.001
Digoxin, n (%)	515 (17)	45 (33)	27 (24)	<0.001
Statin, n (%)	1615 (52)	61 (44)	50 (45)	0.07
Blood tests				
NT-ProBNP (ng/L)	1008 (387-2355)	3319 (1294-7634)	5365 (1907-11284)	<0.001
Hb (g/dL)	13.4 (12.3-14.5)	12.0 (10.7-13.0)	11.6 (10.1-12.8)	<0.001
Urea (mmol/L)	6.7 (5.2-9.2)	7.5 (5.3-11.4)	9.2 (6.5-12.3)	<0.001
Creatinine (µmol/L)	99 (81-124)	111 (83-147)	120 (92-169)	<0.001
Sodium (mmol/L)	139 (137-141)	137 (135-139)	136 (134-139)	<0.001
Potassium (mmol/L)	4.3 (4.1-4.7)	4.3 (3.9-4.6)	4.3 (3.9-4.6)	0.01
Albumin (g/L)	38 (36-40)	31 (30-33)	27 (25-30)	<0.001
Cholesterol (mmol/L)	4.5 (3.8-5.4)	3.9 (3.2-4.6)	3.8 (3.0-4.7)	<0.001
Lymphocyte ($x10^9$/L)	1.3 (1.7-2.1)	1.1 (0.8-1.4)	0.9 (0.6-1.3)	<0.001

ACEi = Angiotensin-converting enzyme inhibitor, AF= atrial fibrillation, SR = sinus rhythm, ARB = Angiotensin receptor blocker, BB= betablocker, BMI= body mass index, BP= blood pressure, COPD = chronic obstructive pulmonary disease, CVD = cerebrovascular disease, PVD = peripheral vascular disease, Hb = Haemoglobin, HeFREF = heart failure with reduced ejection fraction, HR= heart rate, HTN= hypertension, IHD = ischaemic heart disease, MRA = Mineralocorticoids receptor antagonists, NYHA = New York Heart Association Class, NT-proBNP = N-terminal Pro Brain Natriuretic Peptide,

There was no major difference in the prevalence of malnutrition between patients with HeFREF and HeFNEF. According to the CONUT score, 54% of patients with HeFREF and HeFNEF were malnourished. According to GNRI, malnutrition was slightly more common in patients with HeFREF (19%) than HeFNEF (14%). According to PNI, malnutrition was equally common in patients with HeFREF (8%) and HeFNEF (7%) (Table 6.2).

Not surprisingly, the highest prevalence of malnutrition was found in patients who were underweight (BMI<18.5kg/m^2; 1% of the entire CHF cohort). A substantial proportion of patients with BMI ≥30 kg/m^2 (36% of the entire CHF cohort) were malnourished defined by CONUT score (50%) or PNI (5%) but none by GNRI (Table 6.5a). The prevalence of malnutrition measured by any of the 3 tools increased with worsening categories of NT-proBNP (Table 6.5b).

Figure 6.3 summarises the prevalence of malnutrition in different subgroups of patients of patients with CHF (left panel: HeFREF vs HeFNEF and right panel: underweight or normal weight vs overweight or obese).

Table 6.5a: Prevalence of malnutrition in CHF patients by BMI categories (%).

Degree of Malnutrition		**BMI Categories** (kg/m^2)				
		Underweight	**Normal**	**Overweight**	**Obese**	**Morbidly-obese**
		<18.5	18.5-24.9	25.0-29.9	30.0-39.9	≥40
		N=48	N=854	N=1256	N=1061	N=167
CONUT	≥ mild	77	59	54	49	56
	≥ Moderate	21	15	9	7	11
GNRI	≥ mild	96	49	6	0	0
	≥ Moderate	88	20	1	0	0
PNI	≥ Moderate	26	11	7	4	7

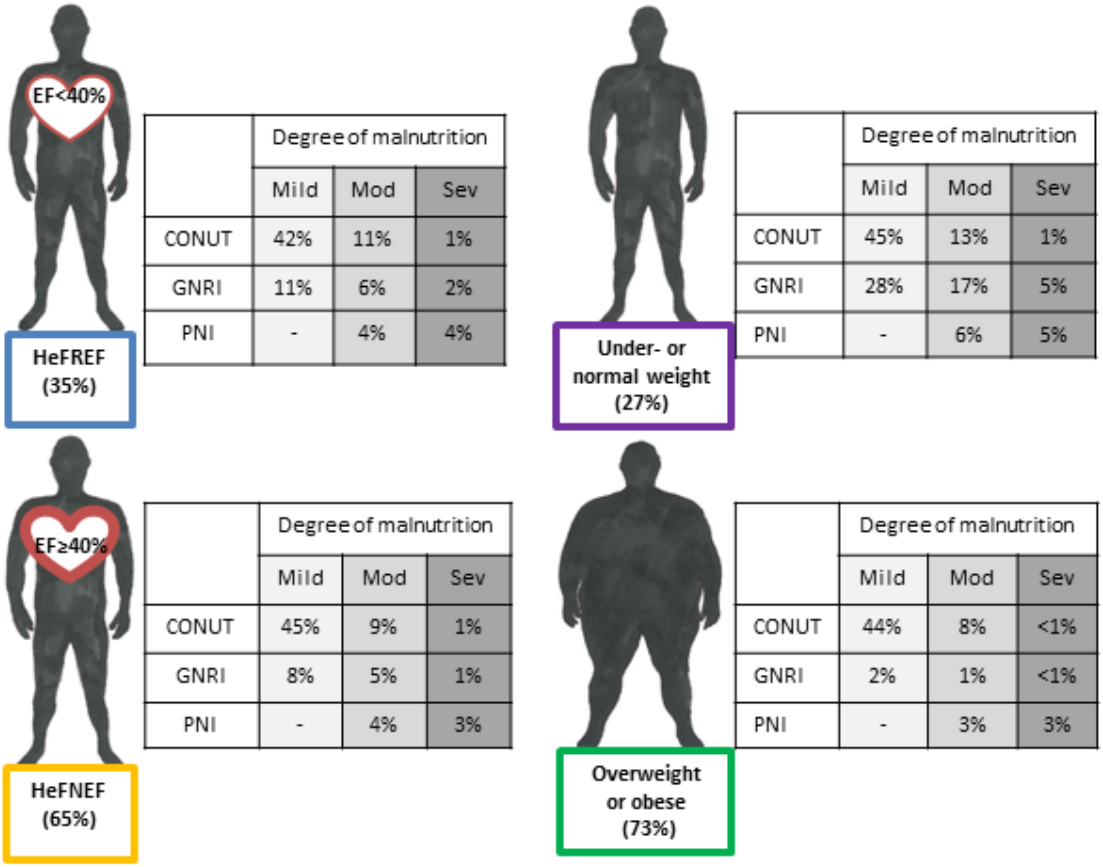
All P<0.001
CONUT = Controlling nutritional status, GNRI = Geriatric nutritional risk index, Prognostic nutritional Index, BMI = body mass index.

Table 6.5b: Prevalence of malnutrition in CHF by NT-proBNP categories. (%)

Degree of Malnutrition		NT-proBNP categories (ng/L) ≤400 N=822	401-1000 N=776	1001-2000 N=697	2001-4000 N=553	>4000 N=538
CONUT	≥ mild	39	47	54	62	78
	≥ Moderate	3	4	8	12	31
GNRI	≥ mild	5	10	15	22	38
	≥ Moderate	2	4	5	7	20
PNI	≥ Moderate	2	3	6	9	23

All P<0.001.
CONUT = Controlling nutritional status, GNRI = Geriatric nutritional risk index, Prognostic nutritional Index, NT-proBNP = N-terminal Pro Brain Natriuretic Peptide.

Figure 6.3: Prevalence of malnutrition in different subgroups of CHF patients.



CONUT = Controlling nutritional status, GNRI = Geriatric nutritional risk index, Prognostic nutritional Index, HeFREF = heart failure with reduced ejection fraction, HeFNEF = heart failure with normal ejection fraction, mod = moderate, sev= severe.

6.4.3 Malnutrition and mortality

During a median follow-up of 1573 days (IQR: 702-2799 days), 1723 (51%) patients died; 351 (10%), 600 (18%) and 818 (24%) after 1, 2 and 3 years respectively. Worsening malnutrition status was associated with worse outcome regardless of the malnutrition tool used (Figures 6.4a-c).

Univariable and multivariable predictors of mortality for the entire CHF cohort and for the different HF phenotypes are shown in table 6.6a-c. Worsening malnutrition was associated with worse outcome regardless of LVEF.

Figure 6.4a. Kaplan Meier curves illustrating the relation between CONUT categories and all-cause mortality.

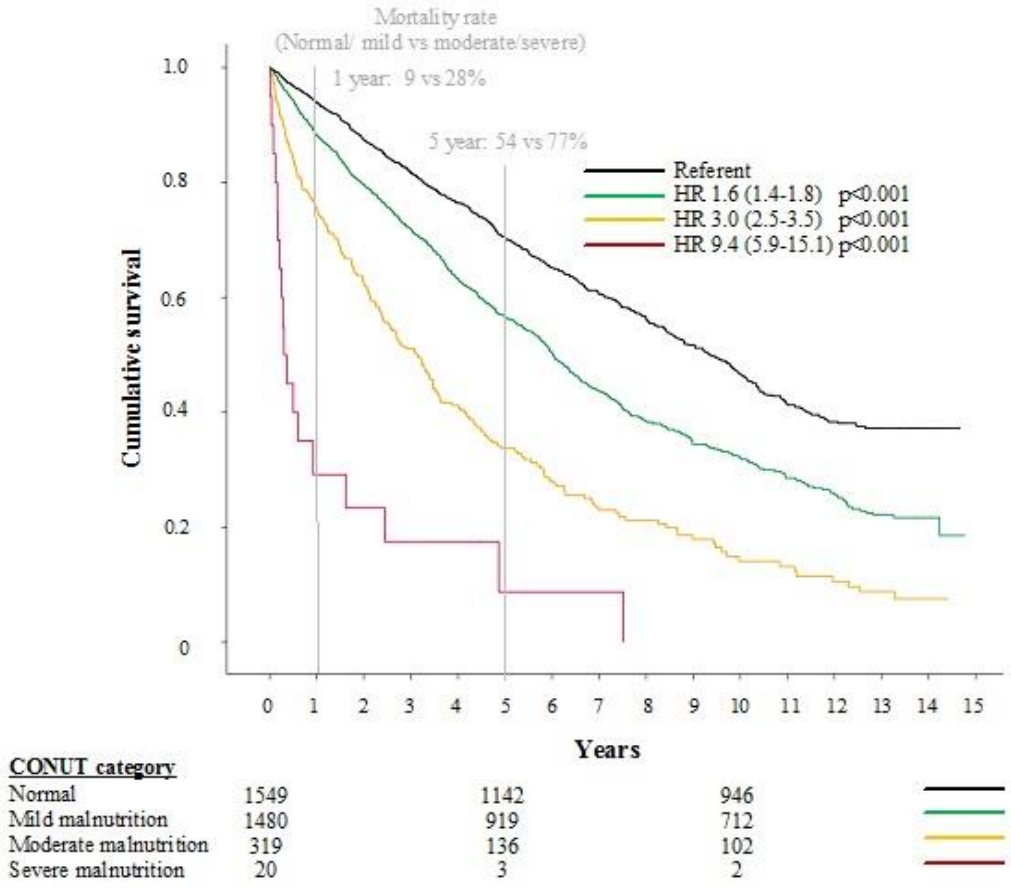


Figure 6.4b. Kaplan Meier curves illustrating the relation between GNRI categories and all-cause mortality.

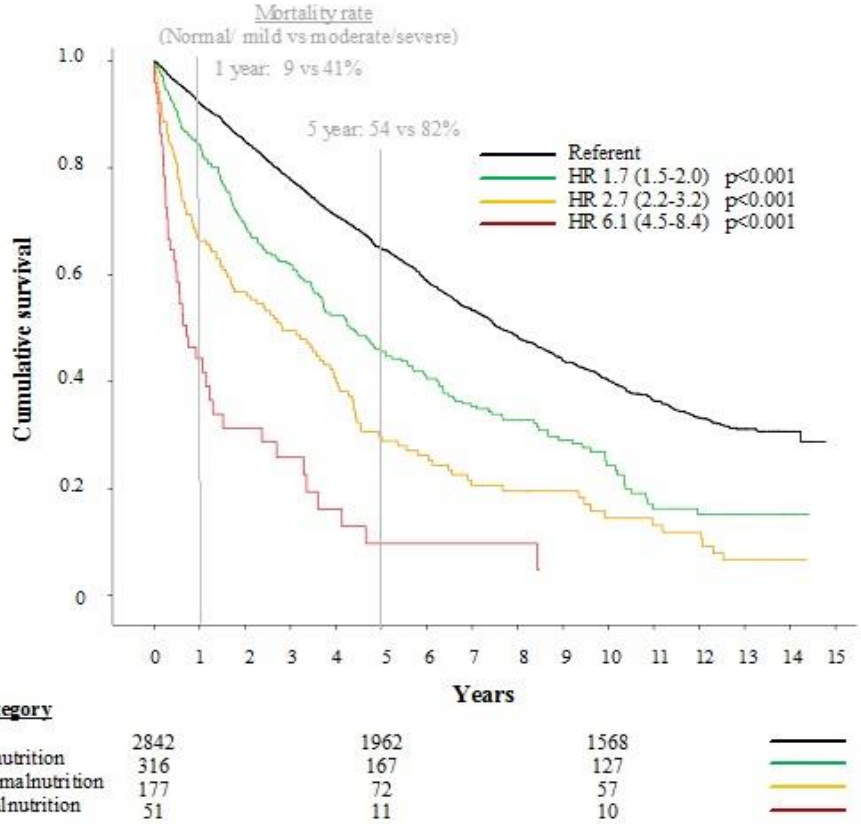


Figure 6.4c. Kaplan Meier curves illustrating the relation between PNI categories and all-cause mortality.

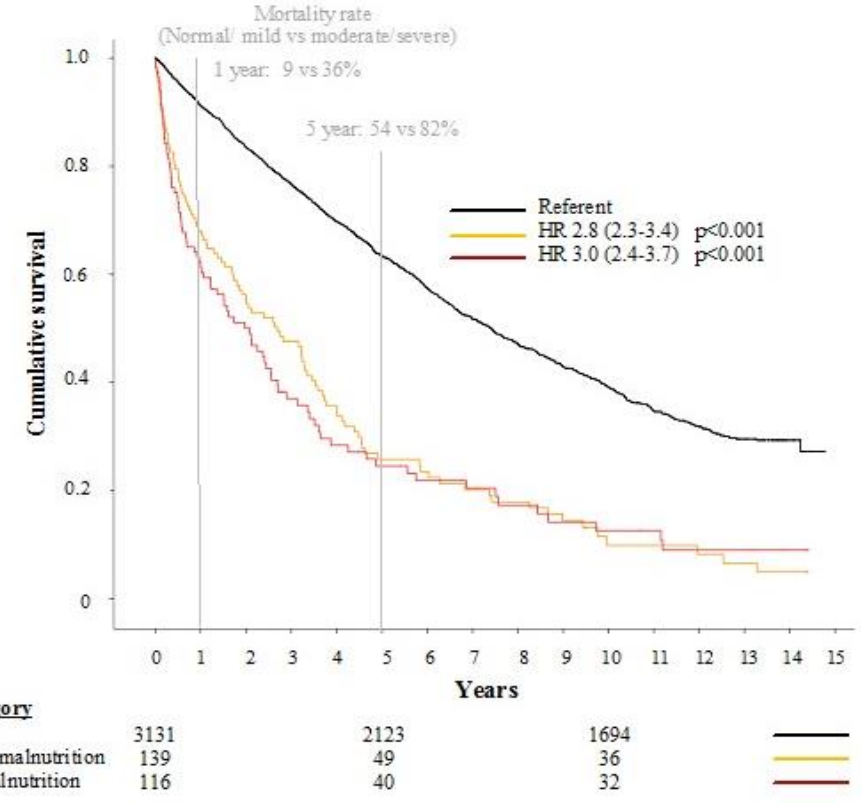


Table 6.6a: Univariable and multivariable analyses of factors predicting all-cause mortality in CHF patients.

Worse outcome per unitary increase	Univariable			Multivariable		
	HR (95%CI)	χ^2	P	HR (95%CI)	χ^2	P
Age (years)	1.06 (1.05-1.06)	362.8	*	1.05 (1.04-1.06)	209.0	*
Sex (male vs female)	1.17 (1.06-1.29)	10.0	0.002	1.29 (1.15-1.45)	18.1	*
BP systolic (mmHg)	0.99 (0.99-1.00)	34.1	*			
BP diastolic (mmHg)	0.98 (0.98-0.98)	129.6	*	0.99 (0.99-1.00)	14.7	*
HR (bpm)	1.01 (1.00-1.01)	22.9	*	1.01 (1.00-1.01)	9.7	0.002
BMI (kg/m^2)	0.97 (0.96-0.98)	41.6	*			
NYHA (III/IV vs I/II)	2.03 (1.84-2.24)	200.7	*	1.56 (1.40-1.74)	64.4	*
CVD (Y vs N)	1.55 (1.31-1.83)	26.8	*			
IHD (Y vs N)	1.11 (1.01-1.22)	4.8	0.03			
PVD (Y vs N)	1.80 (1.48-2.20)	34.0	*	1.66 (1.35-2.05)	22.7	*
AF (Y vs N)	1.32 (1.19-1.47)	26.3	*			
Log [NT-proBNP]	2.80 (2.57-3.06)	524.7	*	1.75 (1.56-1.97)	93.0	*
Hb (g/dL)	0.82 (0.80-0.85)	195.4	*			
Urea (mmol/L)	1.06 (1.05-1.06)	343.2	*	1.03 (1.02-1.04)	21.8	*
Potassium (mmol/L)	1.01 (0.91-1.11)	0.02	0.90			
Sodium (mmol/L)	0.94 (0.93-0.95)	76.8	*			
ACEi/ ARB (Y vs N)	1.00 (0.90-1.11)	0.003	0.96			
BB (Y vs N)	0.70 (0.64-0.77)	53.3	*			
MRA (Y vs N)	1.21 (1.08-1.37)	9.9	0.002			
Loop diuretic (Y vs N)	2.10 (1.90-2.40)	180.6	*			
Digoxin (Y vs N)	1.43 (1.27-1.60)	35.2	*			
CONUT (increasing score)	1.24 (1.21-1.27)	312.1	*			
GNRI (decreasing score)	1.03 (1.02-1.04)	187.2	*	1.26 (1.15-1.37)	27.2	*
PNI (decreasing score)	1.08 (1.07-1.09)	351.2	*			

* P<0.001

Table 6.6b: Univariable and multivariable analyses of factors predicting all-cause mortality in HeFREF patients.

Worse outcome per unitary increase	Univariable			Multivariable		
	HR (95%CI)	χ^2	P	HR (95%CI)	χ^2	P
Age (years)	1.06 (1.05-1.07)	186.3	*	1.05 (1.04-1.06)	79.0	*
Sex (male vs female)	1.07 (0.90-1.27)	0.6	0.44			
BP systolic (mmHg)	0.99 (0.99-1.00)	8.2	0.004			
BP diastolic (mmHg)	0.98 (0.98-0.99)	46.3	*	0.99 (0.98-0.99)	12.4	*
HR (bpm)	1.00 (1.00-1.01)	3.4	0.06			
BMI (kg/m^2)	0.97 (0.95-0.98)	19.5	*			
NYHA (III/IV vs I/II)	1.79 (1.54-2.08)	57.9	*	1.57 (1.33-1.85)	28.9	*
CVD (Y vs N)	1.36 (1.06-1.75)	5.8	0.02			
IHD (Y vs N)	1.36 (1.15-1.60)	13.3	*	1.30 (1.09-1.54)	8.3	0.004
PVD (Y vs N)	1.90 (1.46-2.49)	22.3	*	2.00 (1.50-2.66)	22.4	*
AF (Y vs N)	1.39 (1.17-1.66)	13.4	*			
Log [NT-proBNP]	2.87 (2.49-3.32)	208.3	*	2.03 (1.68-2.46)	53.4	*
Hb (g/dL)	0.85 (0.82-0.89)	55.3	*	0.93 (0.87-0.98)	6.7	0.01
Urea (mmol/L)	1.05 (1.04-1.05)	101.2	*	1.03 (1.01-1.06)	8.0	0.005
Potassium (mmol/L)	0.87 (0.74-1.01)	3.2	0.07			
Sodium (mmol/L)	0.96 (0.94-0.98)	14.1	*			
ACEi/ ARB (Y vs N)	0.86 (0.72-1.04)	2.4	0.12			
BB (Y vs N)	0.69 (0.59-0.80)	23.5	*			
MRA (Y vs N)	0.97 (0.82-1.15)	0.1	0.80			
Loop diuretic (Y vs N)	1.87 (1.54-2.28)	39.8	*			
Digoxin (Y vs N)	1.22 (1.01-1.48)	4.2	0.04			
CONUT (increasing score)	1.19 (1.15-1.23)	90.2	*			
GNRI (decreasing score)	1.03 (1.02-1.04)	70.0	*	1.29 (1.13-1.46)	15.2	*
PNI (decreasing score)	1.06 (1.05-1.07)	94.0	*			

* P<0.001

Table 6.6c: Univariable and multivariable analyses of factors predicting all-cause mortality in HeFNEF patients.

Worse outcome per unitary increase	Univariable			Multivariable		
	HR (95%CI)	χ^2	P	HR (95%CI)	χ^2	P
Age (years)	1.06 (1.05-1.07)	223.2	*	1.05 (1.04-1.06)	109.4	*
Sex (male vs female)	1.22 (1.08-1.39)	1.2	0.001	1.46 (1.26-1.68)	26.6	*
BP systolic (mmHg)	1.00 (0.99-1.00)	14.9	*			
BP diastolic (mmHg)	0.98 (0.98-0.99)	74.8	*	0.99 (0.99-1.00)	4.0	0.05
HR (bpm)	1.01 (1.00-1.01)	18.2	*	1.01 (1.00-1.01)	7.8	0.005
BMI (kg/m^2)	0.98 (0.97-0.99)	18.0	*			
NYHA (III/IV vs I/II)	2.15 (1.89-2.45)	134.6	*	1.33 (1.07-1.66)	6.6	0.01
CVD (Y vs N)	1.67 (1.34-2.08)	20.7	*	1.40 (1.10-1.78)	7.7	0.006
IHD (Y vs N)	0.92 (0.81-1.05)	1.6	0.20	0.85 (0.74-0.98)	4.8	0.03
PVD (Y vs N)	1.62 (1.20-2.17)	10.1	0.001	1.45 (1.06-1.98)	5.4	0.02
AF (Y vs N)	1.33 (1.17-1.53)	17.4	*	1.23 (1.04-1.46)	5.9	0.02
Log [NT-proBNP]	3.06 (2.70-3.47)	303.8	*	1.74 (1.47-2.05)	41.1	*
Hb (g/dL)	0.80 (0.77-0.83)	158.3	*	0.93 (0.89-0.97)	9.8	0.002
Creatinine (umol/L)	1.00 (1.00-1.01)	196.1	*	1.00 (1.00-1.00)	7.9	0.005
Potassium (mmol/L)	1.09 (0.96-1.25)	1.7	0.19			
Sodium (mmol/L)	0.93 (0.91-0.95)	62.9	*	0.97 (0.96-0.99)	6.7	0.01
ACEi/ ARB (Y vs N)	1.00 (0.88-1.13)	0.005	0.94			
BB (Y vs N)	0.68 (0.60-0.77)	37.8	*			
MRA (Y vs N)	1.42 (1.19-1.70)	14.8	*			
Loop diuretic (Y vs N)	2.20 (1.93-2.52)	131.2	*			
Digoxin (Y vs N)	1.58 (1.36-1.83)	36.0	*			
CONUT (increasing score)	1.28 (1.24-1.32)	221.6	*			
GNRI (decreasing score)	1.03 (1.02-1.03)	109.5	*	1.18 (1.05-1.33)	7.4	*
PNI (decreasing score)	1.10 (1.08-1.11)	270.0	*			

* P<0.001

HR = hazard ratio, CI= confidence interval, χ^2= chi-square, ACEi = Angiotensin-converting enzyme inhibitor, AF= atrial fibrillation, ARB = Angiotensin receptor blocker, BB= betablocker, BMI= body mass index, BP= blood pressure, CONUT = Controlling nutritional status, CVD = cerebrovascular disease, GNRI = Geriatric nutritional risk index, Hb = Haemoglobin, HeFNEF = heart failure with normal ejection fraction, HeFREF = heart failure with reduced ejection fraction, HR= heart rate, IHD= ischaemic heart disease, MRA= Mineralocorticoids receptor antagonists, NYHA = New York Heart Association Class, NT-proBNP N-terminal Pro Brain Natriuretic Peptide, PNI = Prognostic nutritional Index, PVD = peripheral vascular disease,Y = yes, N=no.

The following variables were independently associated with adverse outcome in 100% of the 25 prognostic Cox regression models developed using cross-validation: increasing age, urea, log [NT-proBNP], NYHA class (III/IV vs I/II), worse CONUT or GNRI score, male sex, CVD, PVD and diastolic BP; PNI was an independent predictor in 20 models (80%) (Tables 6.7a-b).

Table 6.7a: Cross-validation of prognostic models (*) for CHF patients (medications included).

Variables	**Models**													
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Age (years)	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Sex (male vs female)	*	*	*	*	*	*	*	*	*	*	*	*	*	*
BP systolic (mmHg)														
BP diastolic (mmHg)	*	*	*	*	*	*	*	*	*	*	*	*	*	*
HR (bpm)														
BMI (kg/m^2)														
NYHA (III/IV vs I/II)	*	*	*	*	*	*	*	*	*	*	*	*	*	*
CVD (Y vs N)	*	*	*	*	*	*	*	*	*	*	*	*	*	*
IHD (Y vs N)	*	*	*	*	*	*	*	*	*	*	*	*	*	*
PVD (Y vs N)	*	*	*	*	*	*	*	*	*	*	*	*	*	*
AF (Y vs N)														
Log [NT-proBNP]	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Hb (g/dL)														
Urea (mmol/L)	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Potassium (mmol/L)														
Sodium (mmol/L)			*						*			*	*	*
ACEi/ ARB (Y vs N)														
BB (Y vs N)	*	*	*	*	*	*	*	*	*	*	*	*	*	*
MRA (Y vs N)														
Loop diuretic (Y vs N)	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Digoxin (Y vs N)	*	*			*	*	*	*	*	*	*	*	*	*
CONUT (increasing score)	*	*	*	*	*	*	*	*	*	*	*	*	*	*
GNRI (decreasing score)	*	*	*	*	*	*	*	*	*	*	*	*	*	*
PNI (decreasing score)	*	*		*	*	*	*	*	*	*	*	*	*	*
No. of deaths (all-cause)	1294	1295	1304	1302	1303	1296	1304	1287	1286	1303	1288	1296	1302	1302

Table 6.7a (continued): Cross-validation of prognostic models (*) for CHF patients (medications included).

Variables	**Models**												
	15	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**N**	**%**
Age (years)	*	*	*	*	*	*	*	*	*	*	*	25	100
Sex (male vs female)	*	*	*	*	*	*	*	*	*	*	*	25	100
BP systolic (mmHg)												0	0
BP diastolic (mmHg)	*	*	*	*	*	*	*	*	*	*	*	25	100
HR (bpm)												0	0
BMI (kg/m^2)												0	0
NYHA (III/IV vs I/II)	*	*	*	*	*	*	*	*	*	*	*	25	100
CVD (Y vs N)	*	*	*	*	*	*	*	*	*	*	*	25	100
IHD (Y vs N)	*	*	*	*	*	*	*	*	*	*	*	25	100
PVD (Y vs N)	*	*	*	*	*	*	*	*	*	*	*	25	100
AF (Y vs N)												0	0
Log [NT-proBNP]	*	*	*	*	*	*	*	*	*	*	*	25	100
Hb (g/dL)												0	0
Urea (mmol/L)	*	*	*	*	*	*	*	*	*	*	*	25	100
Potassium (mmol/L)												0	0
Sodium (mmol/L)		*							*			7	28
ACEi/ ARB (Y vs N)												0	0
BB (Y vs N)	*	*	*	*	*	*	*	*	*	*	*	25	100
MRA (Y vs N)												0	0
Loop diuretic (Y vs N)	*	*	*	*	*	*	*	*	*	*	*	25	100
Digoxin (Y vs N)	*	*		*	*	*		*	*	*	*	21	84
CONUT (increasing score)	*	*	*	*	*	*	*	*	*	*	*	25	100
GNRI (decreasing score)	*	*	*	*	*	*	*	*	*	*	*	25	100
PNI (decreasing score)	*	*				*		*	*	*	*	20	80
No. of deaths (all-cause)	128 98	129 0	128 6	129 5	129 9	129 5	129 8	130 5	129 5	130 3	129 9		

Table 6.7b: Cross-validation of prognostic models (*) for CHF patients (medications excluded).

Variables	**Models**													
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Age (years)	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Sex (male vs female)	*	*	*	*	*	*	*	*	*	*	*	*	*	*
BP systolic (mmHg)														
BP diastolic (mmHg)	*	*	*	*	*	*	*	*	*	*	*	*	*	*
HR (bpm)	*	*	*	*	*	*	*	*	*	*	*	*	*	*
BMI (kg/m^2)														
NYHA (III/IV vs I/II)	*	*	*	*	*	*	*	*	*	*	*	*	*	*
CVD (Y vs N)	*	*	*	*	*	*	*	*	*	*	*	*	*	*
IHD (Y vs N)														
PVD (Y vs N)	*	*	*	*	*	*	*	*	*	*	*	*	*	*
AF (Y vs N)														
Log [NT-proBNP]	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Hb (g/dL)					*									
Urea (mmol/L)	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Potassium (mmol/L)														
Sodium (mmol/L)		*		*	*	*						*	*	*
CONUT (increasing score)	*	*	*	*	*	*	*	*	*	*	*	*	*	*
GNRI (decreasing score)	*	*	*	*	*	*	*	*	*	*	*	*	*	*
PNI (decreasing score)	*	*	*	*	*	*	*		*	*	*	*	*	*
No. of deaths (all-cause)	135	131	133	133	133	133	133	133	133	133	133	133	133	133
		1	0	0	0	1	1	1	0	1	0	0	1	0
		1	5	3	9	8	7	8	8	8	2	1	8	3

Table 6.7b (continued): Cross-validation of prognostic models (*) for CHF patients (medications excluded).

Variables	**Models**												
	15	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**N**	**%**
Age (years)	*	*	*	*	*	*	*	*	*	*	*	25	100
Sex (male vs female)	*	*	*	*	*	*	*	*	*	*	*	25	100
BP systolic (mmHg)												0	0
BP diastolic (mmHg)	*	*	*	*	*	*	*	*	*	*	*	25	100
HR (bpm)	*	*	*	*		*	*	*	*	*	*	24	96
BMI (kg/m^2)												0	0
NYHA (III/IV vs I/II)	*	*	*	*	*	*	*	*	*	*	*	25	100
CVD (Y vs N)	*	*	*	*	*	*	*	*	*	*	*	25	100
IHD (Y vs N)												0	0
PVD (Y vs N)	*	*	*	*	*	*	*	*	*	*	*	25	100
AF (Y vs N)												0	0
Log [NT-proBNP]	*	*	*	*	*	*	*	*	*	*	*	25	100
Hb (g/dL)												1	4
Urea (mmol/L)	*	*	*	*	*	*	*	*	*	*	*	25	100
Potassium (mmol/L)												0	0
Sodium (mmol/L)		*				*	*	*		*		12	48
CONUT (increasing score)	*	*	*	*	*	*	*	*	*	*	*	25	100
GNRI (decreasing score)	*	*	*	*	*	*	*	*	*	*	*	25	100
PNI (decreasing score)	*	*	*	*	*				*		*	20	80
No. of deaths (all-cause)	13 10	13 17	13 16	13 12	13 12	13 00	13 09	13 14	13 10	13 12	13 19		

ACEi = Angiotensin-converting enzyme inhibitor, ARB = Angiotensin receptor blocker, AF= atrial fibrillation, BB= betablocker, BMI= body mass index, BP= blood pressure, CONUT = Controlling nutritional status, CVD = cerebrovascular disease, GNRI = Geriatric nutritional risk index, Hb = Haemoglobin, HR= heart rate, IHD = ischaemic heart disease, MRA = Mineralocorticoid receptor antagonists, NT-ProBNP = N-terminal Pro Brain Natriuretic Peptide, NYHA = New York Heart Association Class, PNI = Prognostic nutritional Index, PVD = peripheral vascular disease.

A base model (including age, sex, diastolic BP, heart rate, NYHA class III/IV vs I/II, urea, log [NT-proBNP], CVD and PVD) for predicting mortality achieved a Harrell's C-statistic of 0.719 (Table 6.8). Each malnutrition tool, when added individually, improved the performance of the base model, with GNRI improving model performance most. Addition of BMI (linear or decile) alone did not improve performance of the base model.

Table 6.8: Addition of malnutrition tools and its impact on performance of base model in predicting all-cause mortality.

Model	**Harrell's C-statistic**	**LLR** (improvement from base)	**P** (LLR improvement from base)
Base model*	0.719		-
+ CONUT score	0.721	-16.2	0.001
+ GNRI	0.724	-31.4	<0.001
+ PNI	0.721	-12.1	0.002
+ BMI (linear)	0.719	0	NA
+ BMI (decile)	0.720	-13.0	0.16

*Variables included in the base model: age, sex, diastolic BP, heart rate, New York Heart Association class III/IV vs I/II, urea, log [NT-proBNP], CVD and PVD.

CONUT = Controlling nutritional status, CVD = cerebrovascular disease, GNRI = Geriatric nutritional risk index, NYHA = New York Heart Association, NT-proBNP = N-terminal Pro Brain Natriuretic Peptide, PNI = Prognostic nutritional Index, PVD = peripheral vascular disease, LLR =log-likelihood ratio.

Patients with any degree of malnutrition who were also underweight had the worst outcome. For those with higher BMI, 1-year mortality was substantially higher in the presence of moderate to severe malnutrition by any of the tools used (Table 6.9a). Patients with an NT-proBNP >4000 ng/L and moderate to severe malnutrition had a particularly high 1-year mortality, ranging from 37 to 57% depending on the tool used (Table 6.9b).

Table 6.9a: 1-year mortality (%) of CHF patients by malnutrition and BMI categories.

Degree of Malnutrition		**BMI Categories** (kg/m^2)				
		Underweight <18.5 N=48	**Normal** 18.5-24.9 N=854	**Overweight** 25.0-29.9 N=1256	**Obese** 30.0-39.9 N=1061	**Morbidly-obese** ≥40 N=167
CONUT	None	9	8	6	5	9
	≥ mild	42	17	11	9	5
	≥ Moderate	56	38	23	17	33
GNRI	None	50*	8	9	NA**	NA**
	≥ mild	0*	15	20		
	≥ Moderate	40	41	43		
PNI	None	32	12	9	7	8
	≥ Moderate	50	50	26	24	36

*There are only 2 underweight patients classified as not malnourished by GNRI. There is no underweight patient classified as mildly malnourished by GNRI.
** There is no obese/ morbidly obese patient classified as malnourished by GNRI.

Table 6.9b: 1-year mortality (%) of CHF patients by malnutrition and NT-proBNP categories.

Degree of Malnutrition		**NT-proBNP categories** (ng/L)				
		≤400 N=822	**401-1000** N=776	**1001-2000** N=697	**2001-4000** N=553	**>4000** N=538
CONUT	None	3	5	5	11	20
	≥ mild	4	8	11	12	31
	≥ Moderate	10	19	20	25	37
GNRI	None	3	6	8	12	22
	≥ mild	7	5	13	14	30
	≥ Moderate	29	25	25	28	57
PNI	None	3	6	8	12	25
	≥ Moderate	20	27	26	30	47

CONUT = Controlling nutritional status, GNRI = Geriatric nutritional risk index, Prognostic nutritional Index, BMI = body mass index, NT-proBNP = N-terminal Pro Brain Natriuretic Peptide.

6.5 Discussion

The main finding of this study is that malnutrition, as defined by 3 simple tools, is common in outpatients with CHF and is associated with a poor prognosis regardless of the tool used, and regardless of the LVEF, circulating levels of natriuretic peptides or BMI. Although, malnutrition tools provided only a modest increase in the statistical accuracy of multivariable prognostic models, they may be important for at least two reasons: the wide availability of the variables required for their calculation and malnutrition as a potentially modifiable risk and therapeutic target.

The prevalence of malnutrition is, however, highly dependent upon the tool used, ranging from 8% (by PNI) to 54% (by CONUT score) in the same cohort of patients. Our results are comparable to those from a systematic review on malnutrition tools in HF, which reported the prevalence of malnutrition in patients with CHF to range from 16-62% (118). The differences amongst studies in the prevalence of reported malnutrition might be due either to differences in the severity of HF or the use of different malnutrition tools. In our cohort, concordance amongst tools for mild malnutrition was rather poor, suggesting that they are not interchangeable. However, there was a greater degree of concordance for moderate to severe malnutrition amongst the 3 tools; perhaps reflecting the similarity of the variables on which they are based.

The CONUT score is calculated from variables reflecting protein and lipid metabolism, as well as immune function measured from blood tests. PNI is similar to the CONUT score, but does not include cholesterol. The CONUT score suggested that many more patients with CHF were ‘malnourished’ compared to GNRI or PNI, but this may reflect low plasma cholesterol due to statin therapy. Although the benefits of statins are dubious in HF (167), they are still commonly prescribed, and thus CONUT score is perhaps not the ideal tool. PNI identified far fewer patients as malnourished compared to CONUT score for 2 reasons: firstly, PNI does not include cholesterol; secondly, PNI only identifies patients as either normal or moderately/ severely malnourished; it may therefore underestimate the prevalence of malnutrition.

Amongst the 3 malnutrition tools studied, GNRI had the greatest incremental value in predicting mortality. GNRI is the only tool of the 3 which takes into account both anthropometric factors (the ratio of body weight to ideal body weight) and serum markers

(albumin level). CONUT score and PNI both consider serum markers only. GNRI might be a better malnutrition screening tool than CONUT or PNI because it is multi-dimensional. However, because GNRI considers low body weight to be a marker of malnutrition, it might underestimate malnutrition in overweight patients.

Although our results showed that malnutrition tools improved the performance of prognostic models, the modest increase in C-statistic is of little value for the individual patient. However, given the effect in a substantial population of patients, the increase in C-statistic does emphasise that there is some component of "malnutrition" that is related to prognosis above and beyond the usual clinical variables taken into account when constructing prognostic models. This suggests that there may be some value in further exploring malnutrition, and perhaps its treatment.

In patients with HF, BMI is not an ideal measure of body size and composition, and should not be used as a surrogate of nutritional status. Patients with HF and higher BMI have, on average, lower plasma concentrations of natriuretic peptides and better outcomes than those with lower BMI, a phenomenon sometimes termed the 'obesity paradox' (104). According to the CONUT score and PNI, malnutrition is not only common in underweight patients, but also in those who are overweight, obese, or even morbidly obese. Our results also showed that the malnutrition tools we studied were more highly related to outcome than BMI, and their inclusion in predictive models of outcome improved model performance, whereas including BMI did not. Despite the apparent protective effects of greater BMI, overweight patients who are malnourished according to the CONUT score and PNI, have a higher mortality than those with normal nutritional status, highlighting that malnutrition does not simply manifest as being underweight.

Once present, malnutrition may progress to cachexia, a global wasting process affecting all body compartments including skeletal muscle, fat and bone (91). The causes of cachexia in HF are multifactorial, and might arise as a result of malnutrition, impaired protein and calorie balance, pro-inflammatory immune activation, neurohormonal derangement, physical deconditioning and prolonged immobilisation leading to catabolic anabolic imbalance (91, 168). Screening for malnutrition in patients with HF might enable early identification and characterisation of patients at risk of developing cachexia. Future studies should focus on studying whether better use of available treatments or novel

treatments might improve nutritional status and eventually outcomes in these at-risk HF patients.

6.6 Study limitations

This is a single-centre study which has advantages and disadvantages. It is much easier to develop a system to enrol a large number of consecutive patients and apply consistent criteria and evaluations in a single centre. On the other hand, our patients and processes may differ from other centres. However, variations in patient selection amongst centres, often coupled with poor enrolment, may make multi-centre studies less epidemiologically representative than a well-conducted single centre study. Nonetheless, confirmation of our findings by other investigators in other countries with different healthcare and social systems might be useful. Furthermore, I have only studied 3 of a large number of tools developed to screen for malnutrition. I also did not compare the prognostic value of simple malnutrition tools with more complex multi-dimensional tools (136-138).

Whether it is appropriate to attribute low serum albumin solely to malnutrition is unclear. Hepatic disease and congestion or protein-losing gastrointestinal or renal disease can cause serum albumin to fall. Indeed, points for mild malnutrition according to the CONUT score, appeared to be driven largely by statin therapy. Some of our patients were naïve to, or required optimisation of treatment for HF, which might improve nutritional status, and outcome, particularly in those with HeFREF.

Not everyone will agree with our definition of HeFNEF, for which there is no universal diagnostic agreement. However, malnutrition was much more common and prognosis much worse for patients who fulfilled our definition of HeFNEF compared to patients considered not to have HF.

Furthermore, I did not investigate the changes in nutritional status over time and the relationship between malnutrition and body composition. As reduced mobility occurred significantly in patients with HF who were classified as malnourished, it might also be worthwhile to investigate whether an association between malnutrition and physical deconditioning exists.

6.7 Conclusion

Recognition of the high prevalence and poor prognosis of malnutrition in patients with CHF should stimulate further research into its definition and management. Simple malnutrition tools have a higher prognostic value compared to BMI. This questions the use of BMI as a surrogate of nutritional status in patients with CHF. Further work is needed to clarify how to best evaluate malnutrition in patients with HF.

Chapter 7 Agreement and Classification Performance of Frailty Tools in Patients with Chronic Heart Failure

7.1 Chapter summary

Background: Frailty is common in patients with CHF. There are many frailty tools available but no standard method for evaluating frailty.

Objectives: To compare the prevalence of frailty, agreement and classification performance of 3 frailty assessment tools and 3 screening tools in CHF patients.

Methods: I evaluated frailty using the following screening tools: Clinical frailty scale (CFS); Derby frailty index (DFI); and Acute Frailty Network (AFN) criteria; and the following assessment tools: Fried criteria; Edmonton frailty scale (EFS); and Deficit Index (DI). Since there is no "gold-standard" for frailty evaluation, for each of the frailty tools, I used the results of the other 5 tools to produce a standard combined index. Subjects were 'frail' if so identified by ≥ 3 out of 5 tools.

Results: I studied 467 consecutive ambulatory CHF patients (67% male, median age 76 (IQR: 69-82 years), median NT-proBNP 1156 (IQR: 469-2463) ng/L). The prevalence of frailty in patients with CHF ranged between 30-52%, depending on the tool used.

Frail patients were older, had worse symptoms, higher NT-proBNP and more co-morbidities compared to non-frail patients. Of the screening tools, CFS had the strongest correlation and agreement with the assessment tools (correlation coefficient: 0.86-0.89, kappa coefficient: 0.65-0.72, depending on the frailty assessment tools, all $P<0.001$). CFS had the highest sensitivity (87%) and specificity (89%) amongst screening tools and the lowest misclassification rate (12%) amongst all 6 frailty tools in identifying frailty according to the standard combined frailty index.

Conclusion: Frailty is common in patients with CHF and is associated with increasing age, co-morbidities and severity of HF. CFS is a simple screening tool which identifies a similar group as more lengthy assessment tools.

7.2 Introduction

Frailty is common in patients with CHF and is associated with increased risk of death and hospitalisations (43, 156). However, there is no standard method for evaluating frailty in patients with CHF.

Tools to evaluate frailty stem from two basic concepts of frailty – physical frailty and multi-dimensional frailty.

- The first was proposed by Fried and colleagues, who defined frailty as a physical syndrome using five criteria (Fried criteria): weak grip strength, unintentional weight loss, exhaustion, slow walking speed and low physical activity (44).
- The second concept was proposed by Mitnitski, Rockwood and colleagues, who defined frailty as a state of vulnerability due to accumulation of health deficits (72). Frailty is measured by a Deficit Index (DI) which quantifies the cumulative burden of deficits (77). The Edmonton frailty scale (EFS) is a simplified frailty assessment tool based on the concept of multi-dimensional frailty which has been shown to have good construct validity and reliability (80).

Despite their prognostic value and wide-spread use in research, the Fried criteria and the DI are not routinely used in clinical practice as they are time-consuming to perform: they require physical tests and the evaluation of multiple domains including co-morbidities and social circumstances. Simple screening tools have therefore been developed (84-87). They are much less time-consuming and easier to perform, and might therefore be more useful in busy clinical settings. However, it is not clear whether they identify the same patients as the more comprehensive assessment tools. Very few studies have simultaneously evaluated different tools to quantify frailty in the same cohort of patients with CHF (169, 170).

In this chapter, I will compare the prevalence of frailty, agreement and classification performance of several commonly used frailty tools (3 screening tools vs 3 assessment tools) in a cohort of ambulatory patients with CHF. I will also compare the prevalence of frailty in patients with CHF with those at risk of developing HF.

7.3 Methods

7.3.1 Study population

I prospectively recruited 467 consecutive ambulatory patients with CHF who attended our community HF clinic at Castle Hill Hospital, Hull, UK, between September 2016 and March 2017. All patients had a pre-existing (>1 year) clinical diagnosis of CHF confirmed by either evidence of LVSD on echocardiography or raised NT-proBNP, and had already been initiated on guideline-indicated treatment for HF and were regularly followed up. Patients were phenotyped as HeFREF or HeFNEF according to the HF definitions detailed in Chapter 4. I have only included patients with a pre-existing diagnosis of HF (> 1 year) because studying frailty in stable CHF patients who have been established on optimal HF treatment, reduces the bias associated with a new diagnosis of HF (such as poor symptom control and the potential side-effects of new medications) which might overestimate the prevalence of frailty.

I also prospectively recruited 87 individuals who had previously consented to take part in research at our department as controls. Control subjects were >65 years of age, with no previous or current symptoms or signs of HF and with normal LV systolic function on echocardiography, who also had risk factors for developing HF, including coronary artery disease, diabetes mellitus or HTN.

All patients and controls had a full medical history, a physical examination and blood tests during baseline visit. A detailed description of the study population and relevant examinations can be found in Chapter 4.

7.3.2 Frailty evaluation

I evaluated frailty in CHF patients and controls using the following tools:

- Screening tools:
    1. Derby frailty index (DFI)
    2. Acute Frailty Network criteria (AFN)
    3. Clinical frailty scale (CFS)

- Assessment tools:
    1. Fried criteria
    2. Edmonton frailty scale (EFS)
    3. Deficit index (DI)
- Physical tests:
    1. Handgrip strength
    2. Timed get up and go test (TUGT)
    3. Five meter walk test (5MWT)

The entire frailty evaluation process took 1-1.5 hours per patient. A description of the frailty evaluation process can be found in the 'frailty evaluation' section of Chapter 4.

7.3.3 Statistical analysis

Routine statistical analyses have been detailed in Chapter 4. Firstly, I compared the prevalence of frailty using different tools. Then, I used Venn diagrams to illustrate the relationship amongst frailty tools. Next, I used Kappa statistics to study the agreement amongst frailty tools.

Since there is no gold standard in evaluating frailty in patients with CHF, for each of the screening and assessment tools, I used the results of the *other* 5 tools to produce a single combined frailty index, which I assumed to be the gold standard frailty tool. This methodology has previously been suggested by Pablo and colleagues (171). Similarly, for each of the physical tests, I used the results of the 5 frailty tools which do not include the physical test, to produce a single combined frailty index as the gold standard frailty tool. I defined subjects as frail if so identified by at least 3 of the 5 tools. I then calculated the sensitivity, specificity and predictive values for each of the individual tools and physical tests in identifying frailty according to the combined index.

To investigate the bias associated with CFS being a subjective frailty screening tool, in addition to myself, I also invited a second investigator, a research nurse (JW), to complete the CFS for a random sample of 23 patients. I then used Kappa statistics to determine the inter-operator agreement.

7.4 Results

7.4.1 Baseline characteristics

A total of 467 consecutive patients with CHF and 87 controls was studied. Table 7.1 shows the baseline characteristics of CHF patients vs controls. The majority of patients and controls were male and elderly; 17% of those with CHF were > 85 years (vs 2% of controls). Most of the patients with CHF had HeFREF (62%) with a median NT-proBNP of over 1100ng/L; around one fifth had severe symptoms (NYHA III/IV).

Table 7.1: Baseline characteristics of CHF patients vs controls.

	Controls N=87	**CHF** N=467	Missing	**P**
Demographics				
Age (years)	73 (69-77)	76 (69-82)	0	0.11
Sex (male), n (%)	69 (79)	313 (67)	0	0.02
BP systolic (mmHg)	144 (130-152)	139 (126-162)	0	0.98
BP diastolic (mmHg)	76 (70-82)	75 (66-83)	0	0.40
HR (bpm)	61 (55-70)	70 (60-80)	0	<0.001
Rhythm (AF), n (%)	3 (3)	215 (46)	0	<0.001
Height (m)	1.71 (1.63-1.75)	1.68 (1.61-1.75)	0	0.20
Weight (kg)	81 (73-92)	83 (69-99)	0	0.22
BMI (kg/m^2)	27.8 (25.2-30.8)	29.0 (25.0-33.2)	0	0.08
NYHA III/IV, n (%)	N/A	103 (22)	0	N/A
HeFREF, n (%)	N/A	291 (62)	0	N/A
Moderate LVI		174 (59)		
Moderate-severe LVI		63 (22)		
Severe LVI		54 (19)		
HeFNEF, n (%)	N/A	176 (38)		
Co-morbidities				
MI, n (%)	27 (31)	198 (42)	0	0.05
PVD, n (%)	16 (18)	72 (15)	0	0.49
HTN, n (%)	61 (70)	313 (67)	0	0.57
CVD, n (%)	5 (6)	71 (15)	0	0.02

Table 7.1 (continued): Baseline characteristics of CHF patients vs controls.

	Controls N=87	**CHF** N=467	Missing	**P**
Co-morbidities				
Diabetes Mellitus, n (%)	35 (40)	163 (35)	0	0.24
Dementia, n (%)	1 (1)	48 (10)	0	0.006
COPD, n (%)	16 (18)	140 (30)	0	0.03
Depression, n (%)	9 (10)	93 (20)	0	0.03
Anaemia, n (%)	22 (25)	218 (47)	0	<0.001
Falls, n (%)	5 (6)	173 (37)	0	<0.001
Urinary incontinence, n (%)	1 (1)	33 (7)	0	0.04
Charlson Score	6 (4-7)	8 (6-10)	0	<0.001
Medications				
ACEi/ARB, n (%)	51 (59)	389 (83)	0	<0.001
BB, n (%)	57 (66)	392 (84)	0	<0.001
MRA, n (%)	1 (1)	214 (46)	0	<0.001
Loop diuretics, n (%)	3 (3)	347 (74)	0	<0.001
Thiazide diuretics, n (%)	8 (9)	17 (4)	0	0.02
Digoxin, n (%)	0	100 (21)	0	<0.001
≥5 medications, n (%)	58 (67)	404 (87)	0	<0.001
Blood tests				
NT-ProBNP (ng/L)	170 (99-278)	1156 (496-2463)	2	<0.001
Hb (g/dL)	13.9 (12.7-14.7)	13.1 (11.8-14.2)	0	0.007
Sodium (mmol/L)	137 (136-139)	137 (135-138)	0	0.10
Potassium (mmol/L)	4.4 (4.2-4.6)	4.4 (4.2-4.7)	0	0.11
eGFR (ml/min/1.73 m^2)	77 (64-87)	55 (40-73)	0	<0.001

HR= heart rate, BP= blood pressure, NYHA= New York Heart Association, LVI= left ventricular impairment, BMI= body mass index, MI= myocardial infarction, PVD= peripheral vascular disease, HTN= hypertension, CVD= cerebrovascular disease, AF= atrial fibrillation, COPD= chronic obstructive pulmonary disease, BB= beta-blocker, ACEi= angiotensin converting enzyme inhibitor, ARB= angiotensin receptor blocker, MRA= mineralocorticoid receptor antagonist, NT-proBNP= N-terminal pro-B-type natriuretic peptide, Hb= haemoglobin, eGFR = estimated glomerular filtration rate, N/A = not applicable.

7.4.2 Prevalence of frailty

The prevalence of frailty varied according to the frailty tool used. Frailty was much more common in CHF patients than in controls, regardless of the tool used (CHF: 30-52% vs

controls: 2-15%) (Table 7.2). For this reason, I focused the rest of this chapter on studying frailty in CHF patients.

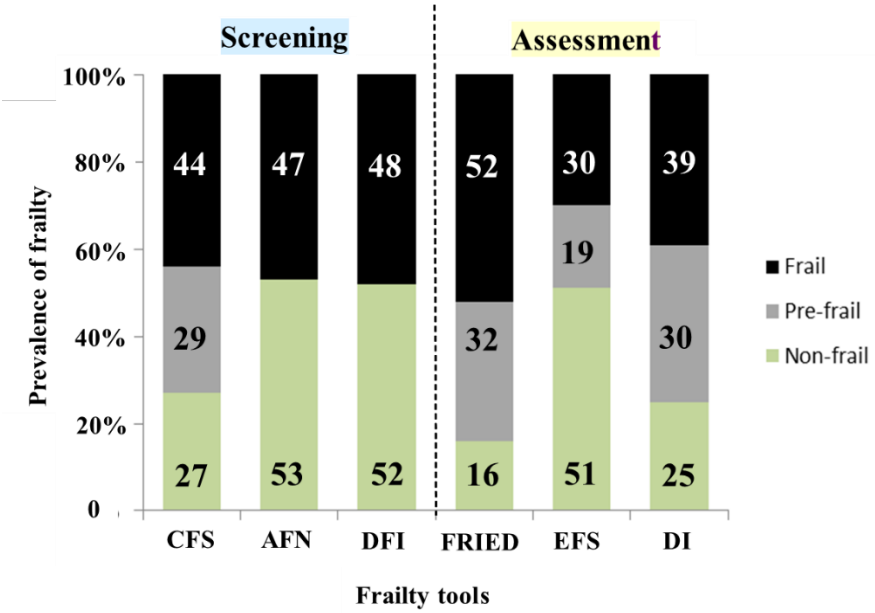
Table 7.2: Prevalence of frailty in CHF patients vs controls.

	Assessment tools				Screening tools		
	Fried ≥3 (N=250)	**DI** upper tertile (N=193) 0.40-0.49	**DI** upper tertile (N=193) ≥ 0.5	**EFS** ≥8 (N=142)	**CFS** >4 (N=209)	**AFN** Frail (N=230)	**DFI** Frail (N=230)
CHF (N=467)	52% (N=244)	35% (N=57)	29% (N=48)	30% (N=140)	44% (N=206)	47% (N=217)	48% (N=224)
Controls (N=87)	7% (N=6)	7% (N=2)	4% (N=1)	2% (N=2)	3% (N=3)	15% (N=13)	7% (N=6)
P (CHF vs controls)	<0.001	NA		<0.001	<0.001	<0.001	<0.001

Fried= fried criteria, DI= deficit index, EFS= Edmonton frailty scale, CFS= clinical frailty scale, AFN= acute frailty network frailty criteria, DFI= derby frailty index.

Amongst the frailty assessment tools, Fried criteria scored the greatest proportion of patients as frail (52%) while EFS scored the lowest proportion as frail (30%) (Figure 7.1). 26% (N=119) of patients were classified as frail by all 3 assessment tools (Figure 7.2).

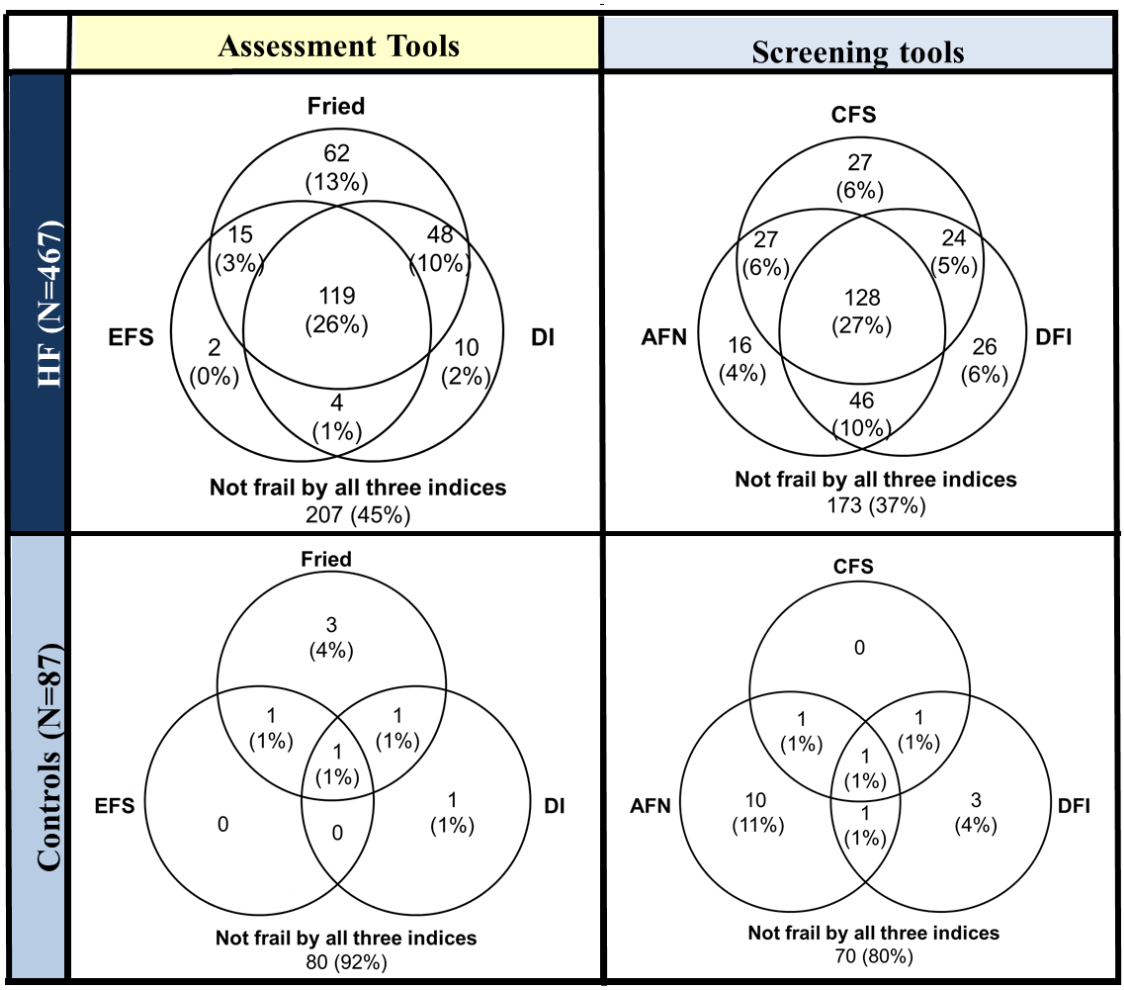
Figure 7.1: Prevalence of frailty and pre-frailty in CHF patients.



Fried= fried criteria, DI= deficit index, EFS= Edmonton frailty scale, CFS= clinical frailty scale, AFN= acute frailty network frailty criteria, DFI= derby frailty index.

Amongst the frailty screening tools, DFI scored the greatest proportion of patients as frail (48%) while CFS scored the lowest proportion as frail (44%) (Figure 7.1). 27% (N=128) of patients were classified as frail by all 3 screening tools (Figure 7.2).

Figure 7.2: Relationship amongst frailty tools in detecting frailty in CHF patients vs controls.



Fried= fried criteria, DI= deficit index, EFS= Edmonton frailty scale, CFS= clinical frailty scale, AFN= acute frailty network frailty criteria, DFI= derby frailty index.

The prevalence of frailty was higher in patients with HeFNEF compared to those with HeFREF (Table 7.3). The prevalence of frailty was higher in patients with AF compared to those in SR. The prevalence of frailty increased with decreasing BMI and increasing NYHA class, age and NT-proBNP.

Table 7.3: Prevalence of frailty in different subgroups of CHF patients.

		Assessment tools			Screening tools		
		Fried (N=250)	**DI** (N=165)	**EFS** (N=142)	**CFS** (N=209)	**AFN** (N=230)	**DFI** (N=230)
Rhythm	**SR** (N=252)	46% (N=116)	32% (N=80)	25% (N=64)	39% (N=98)	40% (N=100)	43% (N=108)
	AF (N=215)	60% (N=128)	40% (N=85)	35% (N=76)	50% (N=108)	54% (N=117)	54% (N=116)
	P	0.004	0.02	0.02	0.02	0.001	0.02
BMI (kg/m^2)	**<24.9** (N=111)	60% (N=67)	41% (N=46)	41% (N=46)	53% (N=59)	62% (N=69)	64% (N=71)
	25.0-29.9 (N=158)	50% (N=79)	30% (N=48)	25% (N=39)	42% (N=66)	45% (N=71)	54% (N=86)
	≥30 (N=198)	50% (N=98)	36% (N=71)	28% (N=55)	41% (N=81)	39% (N=77)	34% (N=67)
	P	0.15	0.17	0.009	0.09	<0.001	<0.001
HF phenotype	**HeFREF** (N=291)	47% (N=138)	31% (N=90)	27% (N=79)	40% (N=117)	39% (N=114)	42% (N=122)
	HeFNEF (N=176)	60% (N=106)	43% (N=75)	35% (N=61)	51% (N=89)	59% (N=103)	58% (N=102)
	P	0.007	0.01	0.09	0.03	<0.001	0.001
NYHA*	**I/II** (N=364)	44% (N=159)	28% (N=102)	22% (N=81)	35% (N=128)	40% (N=145)	42% (N=154)
	III/IV (N=103)	83% (N=85)	61% (N=63)	57% (N=59)	76% (N=78)	70% (N=72)	68% (N=70)
NT-proBNP * (ng/L)	**<1000** (N=215)	41% (N=88)	26% (N=56)	22% (N=47)	33% (N=70)	32% (N=68)	35% (N=76)
	1000-2000 (N=108)	55% (N=59)	35% (N=38)	30% (N=32)	45% (N=49)	52% (N=56)	54% (N=58)
	>2000 (N=144)	67% (N=97)	49% (N=71)	42% (N=61)	60% (N=87)	65% (N=93)	63% (N=90)
Age (years)*	**<65** (N=82)	28% (N=23)	20% (N=16)	12% (N=10)	22% (N=18)	NA	NA
	65-75 (N=139)	35% (N=49)	23% (N=32)	18% (N=25)	27% (N=38)	32% (N=44)	9% (N=13)
	>75 (N=246)	70% (N=172)	48% (N=117)	43% (N=105)	61% (N=150)	70% (N=173)	86% (N=211)

*P<0.001. Fried= fried criteria, DI= deficit index, EFS= Edmonton frailty scale, CFS= clinical frailty scale, AFN= acute frailty network frailty criteria, DFI= derby frailty index, SR= sinus rhythm, AF= atrial fibrillation, BMI= body mass index, HeFREF= heart failure with reduced ejection fraction, HeFNEF= heart failure with normal ejection fraction, NYHA= New York Heart Association, NT-proBNP= N-terminal pro B type natriuretic peptide.

7.4.3 Prevalence of pre-frailty

The prevalence of pre-frailty varied greatly depending on the assessment tool used. (Table 7.4) According to the EFS, the prevalence of pre-frailty was much higher in patients than controls, but according to the Fried criteria, pre-frailty was as common in both groups.

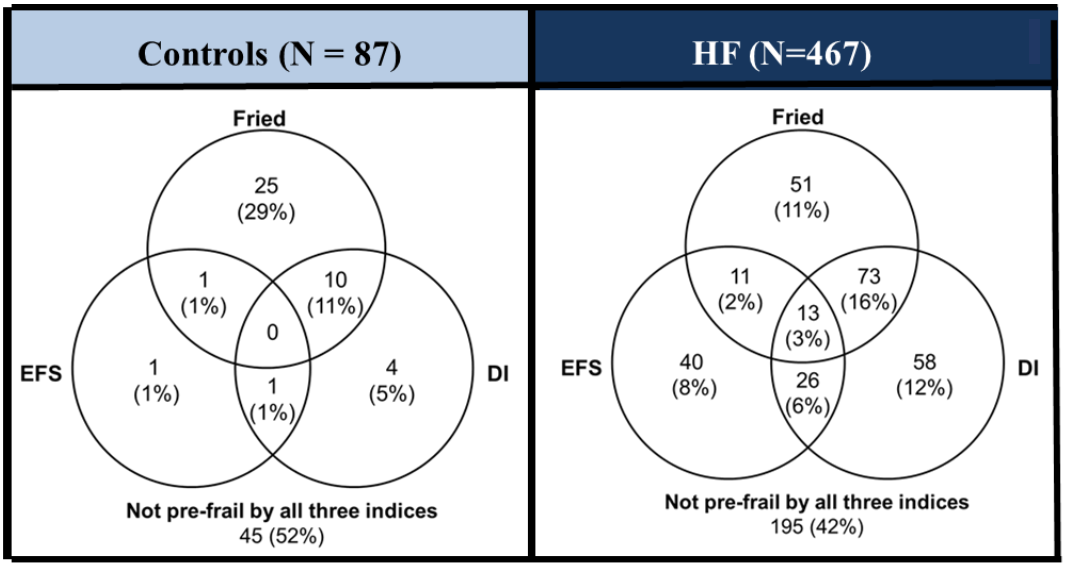
Table 7.4: Prevalence of pre-frailty in CHF patients vs controls.

	Assessment tools			
	Fried 1-2 (N=184)	**DI** middle tertile (N=177) <0.15	<0.25	**EFS** 6-7 (N=93)
CHF (N=467)	32% (N=148)	0	22% (N=32)	19% (N=90)
Controls (N=87)	41% (N=36)	70% (N=21)	100% (N=30)	3% (N=3)
P (CHF vs controls)	0.08	NA		<0.001

Fried= fried criteria, DI= deficit index, EFS= Edmonton frailty scale, CFS= clinical frailty scale, AFN= acute frailty network frailty criteria, DFI= derby frailty index.

The Fried criteria scored the greatest proportion of patients as pre-frail (32%) while the EFS scored the lowest proportion as pre-frail (19%) (Table 7.4). Only 3% (N=13) of patients were classified as 'pre-frail' by all 3 assessment tools (Figure 7.3).

Figure 7.3: Relationship amongst frailty tools in detecting pre-frailty in CHF patients vs controls.



7.4.4 Relation between frailty and clinical data

Compared to those who are not frail, frail patients were older, had worse symptoms, higher NT-proBNP, worse renal function and anaemia. They were more likely to be on diuretics but less likely to be on an ACEi/ARB, a beta-blocker or an MRA; they also had a lower BMI and more co-morbidities: especially dementia, COPD, depression, recurrent falls and urinary incontinence (Table 7.5a-c).

Table 7.5a: Baseline characteristics of frail vs non-frail CHF patients by Fried criteria.

	Non-frail N=223	**Frail** N=244	**P**
Demographics			
Age (years)	72 (64-78)	80 (74-84)	<0.001
Sex (male), n (%)	165 (74)	148 (61)	0.002
BP systolic (mmHg)	140 (125-157)	138 (126-166)	0.17
BP diastolic (mmHg)	74 (67-83)	75 (65-83)	0.35
HR (bpm)	70 (61-77)	71 (60-82)	0.14
Height (m)	1.70 (1.64-1.76)	1.66 (1.59-1.74)	<0.001
Weight (kg)	86 (74-102)	79 (66-96)	0.006
BMI (kg/m^2)	29.4 (26.0-33.3)	28.7 (24.4-32.8)	0.15
NYHA III/IV, n (%)	18 (8)	85 (35)	<0.001
HeFREF, n (%)	153 (69)	138 (57)	0.007
HeFNEF, n (%)	70 (31)	106 (43)	
Co-morbidities			
MI, n (%)	98 (44)	100 (41)	0.52
PVD, n (%)	28 (13)	44 (18)	0.10
HTN, n (%)	139 (62)	174 (71)	0.04
CVD, n (%)	22 (10)	49 (20)	0.002
Diabetes Mellitus, n (%)	69 (31)	94 (39)	0.05
Dementia, n (%)	4 (2)	44 (18)	<0.001
COPD, n (%)	47 (21)	93 (38)	<0.001
Depression, n (%)	28 (13)	65 (27)	<0.001
Anaemia, n (%)	77 (35)	141 (58)	<0.001

Table 7.5a (continued): Baseline characteristics of frail vs non-frail CHF patients by Fried criteria.

	Non-frail N=223	**Frail** N=244	**P**
Co-morbidities			
Falls, n (%)	32 (14)	141 (58)	<0.001
Urinary incontinence, n (%)	8 (4)	25 (10)	0.005
Charlson Score	7 (5-9)	9 (8-11)	<0.001
Medications			
ACEi/ARB, n (%)	202 (91)	187 (77)	<0.001
BB, n (%)	201 (90)	191 (78)	<0.001
MRA, n (%)	109 (49)	105 (43)	0.21
Loop diuretics, n (%)	146 (66)	201 (82)	<0.001
Thiazide diuretics, n (%)	4 (2)	13 (5)	0.04
Digoxin, n (%)	42 (19)	58 (24)	0.19
≥5 medications, n (%)	176 (79)	228 (93)	<0.001
Blood tests			
NT-proBNP (ng/L)	1020 (436-2124)	2465 (1372-4143)	<0.001
Hb (g/dL)	13.2 (12.0-14.3)	12.1 (11.0-13.1)	<0.001
Sodium (mmol/L)	137 (135-138)	136 (133-138)	0.05
Potassium (mmol/L)	4.4 (4.2-4.7)	4.3 (4.1-4.8)	0.32
eGFR (ml/min/1.73 m^2)	59 (37-76)	55 (40-73)	0.99

Table 7.5b: Baseline characteristics of frail vs non-frail CHF patients by DI.

	Non-frail N=302	**Frail** N=165	**P**
Demographics			
Age (years)	74 (66-80)	80 (74-85)	<0.001
Sex (male), n (%)	214 (71)	99 (60)	0.02
BP systolic (mmHg)	140 (125-158)	137 (128-167)	0.15
BP diastolic (mmHg)	75 (67-83)	74 (65-83)	0.43
HR (bpm)	70 (60-80)	70 (62-82)	0.80
Height (m)	1.70 (1.63-1.75)	1.65 (1.59-1.74)	0.001
Weight (kg)	84 (72-99)	78 (66-97)	0.05
BMI (kg/m^2)	29.1 (25.6-33.2)	28.8 (24.3-33.1)	0.52
NYHA III/IV, n (%)	40 (13)	63 (38)	<0.001
HeFREF, n (%)	201 (67)	90 (54)	0.10
HeFNEF, n (%)	101 (33)	75 (46)	
Co-morbidities			
MI, n (%)	121 (40)	77 (47)	0.17
PVD, n (%)	34 (11)	38 (23)	0.001
HTN, n (%)	192 (64)	121 (73)	0.03
CVD, n (%)	26 (9)	45 (27)	<0.001
Diabetes Mellitus, n (%)	90 (30)	73 (44)	0.002
Dementia, n (%)	8 (3)	40 (24)	<0.001
COPD, n (%)	73 (24)	67 (41)	<0.001
Depression, n (%)	42 (14)	51 (31)	<0.001
Anaemia, n (%)	110 (36)	108 (66)	<0.001
Falls, n (%)	63 (21)	110 (67)	<0.001
Urinary incontinence, n (%)	11 (4)	22 (13)	0.001
Charlson Score	7 (5-9)	10 (9-12)	<0.001

Table 7.5b (continued): Baseline characteristics of frail vs non-frail CHF patients by DI.

	Non-frail N=302	**Frail** N=165	**P**
Medications			
ACEi/ARB, n (%)	274 (91)	115 (70)	<0.001
BB, n (%)	263 (87)	129 (78)	0.01
MRA, n (%)	153 (51)	61 (37)	0.005
Loop diuretics, n (%)	213 (71)	134 (81)	0.01
Thiazide diuretics, n (%)	5 (2)	12 (7)	0.002
Digoxin, n (%)	69 (23)	31 (19)	0.31
≥5 medications, n (%)	247 (82)	157 (95)	<0.001
Blood tests			
NT-proBNP (ng/L)	919 (402-1899)	1669 (812-3426)	<0.001
Hb (g/dL)	13.5 (12.3-14.4)	12.1 (11.2-13.4)	<0.001
Sodium (mmol/L)	137 (135-138)	136 (134-138)	0.09
Potassium (mmol/L)	4.5 (4.2-4.7)	4.4 (4.1-4.7)	0.11
eGFR (ml/min/1.73 m^2)	61 (45-76)	48 (32-63)	0.004

Table 7.5c: Baseline characteristics of frail vs non-frail CHF patients by EFS.

	Non-frail N=327	**Frail** N=140	**P**
Demographics			
Age (years)	74 (66-80)	80 (75-85)	<0.001
Sex (male), n (%)	224 (69)	89 (64)	0.30
BP systolic (mmHg)	141 (126-162)	137 (125-162)	0.79
BP diastolic (mmHg)	75 (67-83)	73 (64-82)	0.02
HR (bpm)	70 (60-79)	70 (61-83)	0.21
Height (m)	1.69 (1.62-1.75)	1.65 (1.59-1.74)	0.003
Weight (kg)	84 (72-99)	78 (64-97)	0.003
BMI (kg/m^2)	29.1 (25.8-33.3)	28.6 (23.6-32.7)	0.07
NYHA III/IV, n (%)	44 (14)	59 (42)	<0.001
HeFREF, n (%)	212 (65)	79 (56)	0.09
HeFNEF, n (%)	115 (35)	61 (44)	
Co-morbidities			
MI, n (%)	142 (43)	56 (40)	0.49
PVD, n (%)	42 (13)	30 (21)	0.02
HTN, n (%)	221 (68)	92 (66)	0.69
CVD, n (%)	37 (11)	34 (24)	<0.001
Diabetes Mellitus, n (%)	106 (33)	57 (41)	0.21
Dementia, n (%)	5 (2)	43 (31)	<0.001
COPD, n (%)	78 (24)	62 (44)	<0.001
Depression, n (%)	48 (15)	45 (32)	<0.001
Anaemia, n (%)	126 (39)	92 (66)	<0.001
Falls, n (%)	83 (25)	90 (64)	<0.001
Urinary incontinence, n (%)	13 (4)	20 (14)	<0.001
Charlson Score	8 (6-9)	10 (8-12)	<0.001

Table 7.5c (continued): Baseline characteristics of frail vs non-frail CHF patients by EFS.

	Non-frail N=327	**Frail** N=140	**P**
Medications			
ACEi/ARB, n (%)	291 (89)	98 (70)	<0.001
BB, n (%)	280 (86)	112 (80)	0.13
MRA, n (%)	162 (50)	52 (37)	0.01
Loop diuretics, n (%)	230 (70)	117 (84)	0.003
Thiazide diuretics, n (%)	9 (3)	8 (6)	0.12
Digoxin, n (%)	69 (21)	31 (22)	0.80
≥5 medications, n (%)	269 (82)	135 (96)	<0.001
Blood tests			
NT-proBNP (ng/L)	963 (426-1919)	2613 (1013-4712)	<0.001
Hb (g/dL)	13.4 (12.1-14.4)	12.0 (10.9-13.1)	<0.001
Sodium (mmol/L)	137 (135-138)	136 (134-138)	0.22
Potassium (mmol/L)	4.5 (4.2-4.7)	4.3 (4.1-4.6)	0.007
eGFR (ml/min/1.73 m^2)	56 (41-74)	52 (33-70)	0.02

HR= heart rate, BP= blood pressure, NYHA= New York Heart Association, HeFREF= heart failure with reduced ejection fraction, HeFNEF= heart failure with normal ejection fraction, BMI= body mass index, MI= myocardial infarction, PVD= peripheral vascular disease, HTN= hypertension, CVD= cerebrovascular disease, COPD= chronic obstructive pulmonary disease, BB= beta-blocker, ACEi= angiotensin converting enzyme inhibitor, ARB= angiotensin receptor blocker, MRA= mineralocorticoid receptor antagonist, NT-proBNP= N-terminal pro-B-type natriuretic peptide, Hb= haemoglobin, eGFR = estimated glomerular filtration rate.

Compared to those who were classified as frail by 1 or 2 assessment tools, patients who were classified as frail by all 3 assessment tools were older, had worse symptoms, more severe HF, lower Hb and higher co-morbidity burden (Table 7.6).

Table 7.6: Characteristics of CHF patients classified as frail by all 3 assessment tools vs those classified as frail by 1 or 2 assessment tools.

	Frail by		P
	All 3 assessment tools N=119	1 or 2 assessment tools N=141	
Age (years)	81 (76-86)	78 (72-84)	0.02
NT-proBNP (ng/L)	1713 (883 -3702)	1375 (693-2579)	0.03
Hb (g/dL)	12.0 (10.9-13.1)	13.0 (12.0-14.0)	<0.001
eGFR (ml/min/1.73 m^2)	47 (32-65)	53 (38-68)	0.13
HeFREF, n (%)	63 (53)	87 (62)	0.18
NYHA III/IV, n (%)	54 (46)	35 (25)	<0.001
Charlson score	10 (9-12)	9 (7-10)	<0.001

NYHA= New York Heart Association, HeFREF= heart failure with reduced ejection fraction, NT-proBNP= N-terminal pro-B-type natriuretic peptide, Hb= haemoglobin, eGFR = estimated glomerular filtration rate.

7.4.5 Relation amongst frailty tools

The relation amongst frailty tools is shown in Table 7.7. Of the 3 frailty *screening* tools, CFS had the strongest correlation with the frailty *assessment* tools (correlation coefficient: 0.86-0.89, depending on the frailty assessment tools, all P<0.001)

Table 7.7: Correlation coefficients for frailty tools.

Tools		Screening			Assessment	
		DFI	AFN	CFS	Fried	EFS
Screening	AFN	0.60				
	CFS	0.54	0.59			
Assessment	Fried	0.54	0.57	0.86		
	EFS	0.50	0.56	0.89	0.81	
	DI	0.48	0.53	0.87	0.77	0.86

All P< 0.001. AFN= acute frailty network frailty criteria, DFI= derby frailty index, CFS= clinical frailty scale, Fried = Fried criteria, EFS= Edmonton frailty scale, DI= deficit index.

7.4.6 Detection of frailty: screening vs assessment tools

Of the screening tools, CFS had the highest and DFI the lowest agreement with the assessment tools in distinguishing between frail and non-frail patients (Table 7.8).

Table 7.8: Agreement amongst frailty screening vs assessment tools.

Frailty tools			**SCREENING**					
			CFS		AFN		DFI	
			NF (N=261)	F (N=206)	NF (N=250)	F (N=217)	NF (N=243)	F (N=224)
ASSESSMENT	FRIED	NF (N=223)	45% (N=209)	3% (N=14)	38% (N=178)	10% (N=45)	37% (N=172)	11% (N=51)
		F (N=244)	11% (N=52)	41% (N=192)	15% (N=72)	37% (N=172)	15% (N=71)	37% (N=173)
			K= 0.72		K= 0.50		K= 0.48	
	DI	NF (N=302)	54% (N=250)	11% (N=52)	46% (N=214)	19% (N=88)	42% (N=197)	22% (N=105)
		F (N=165)	2% (N=11)	33% (N=154)	8% (N=36)	27% (N=129)	10% (N=46)	26% (N=119)
			K= 0.72		K= 0.46		K= 0.35	
	EFS	NF (N=327)	55% (N=255)	15% (N=72)	48% (N=225)	22% (N=102)	45% (N=209)	25% (N=118)
		F (N=140)	1% (N=6)	29% (N=134)	5% (N=25)	25% (N=115)	7% (N=34)	23% (N=106)
			K= 0.65		K= 0.44		K= 0.34	

All P<0.001. NF = non-frail, F=frail, CFS= clinical frailty scale, AFN= acute frailty network frailty criteria, DFI= derby frailty index, Fried= fried criteria, DI= deficit index, EFS= Edmonton frailty scale, K= kappa coefficient.

7.4.7 Frailty tools versus combined index

Table 7.9a-c show the sensitivity, specificity and misclassification rates of different frailty tools (screening vs assessment vs single physical tests) in identifying frailty according to the combined index (the presumed gold standard for identifying frailty).

Of the screening tools, CFS had the highest sensitivity (87%) and specificity (89%). DFI had the highest false positive rate (16%) and false negative rate (10%). CFS had the lowest misclassification rate (12%) (Table 7.9a).

Of the assessment tools, the Fried criteria had the highest sensitivity (93%) and EFS had the highest specificity (98%). The Fried criteria had the highest false positive rate (14%) and EFS has the highest false negative rate (18%) (Table 7.9b).

Of the three single physical tests, TUGT had the highest sensitivity (97%) and 5MWT test had the highest specificity (59%). Handgrip strength had the highest false positive rate (25%) and false negative rate (3%). Overall, TUGT had the lowest misclassification rate (25%) (Table 7.9c).

Compared to frailty assessments or screening tools, single physical tests had higher overall sensitivities but lower specificities and higher misclassification rates.

Table 7.9a: Performance of screening tools in identifying frailty according to the combined index.

	Screening		
	CFS >4	AFN (Frail)	DFI (Frail)
Sensitivity (%)	87	79	76
Specificity (%)	89	78	73
PPV (%)	86	72	67
NPV (%)	90	83	81
False positive (%)	6	13	16
False negative (%)	6	9	10
Misclassification rate (%)	12	22	26

Table 7.9b: Performance of assessment tools in identifying frailty according to the combined index.

	Assessment		
	Fried ≥3	EFS≥8	DI (upper tercile)
Sensitivity (%)	93	62	75
Specificity (%)	76	98	92
PPV (%)	73	96	88
NPV (%)	94	74	81
False positive (%)	14	1	5
False negative (%)	3	18	12
Misclassification rate (%)	17	19	17

Table 7.9c: Performance of physical tests in identifying frailty according to the combined index.

	Physical tests		
	Hand grip*	5MWT*	TUGT >10sec
Sensitivity (%)	93	95	97
Specificity (%)	58	59	55
PPV (%)	61	62	66
NPV (%)	92	94	96
False positive (%)	25	24	24
False negative (%)	3	2	1
Misclassification rate (%)	28	26	25

* Frail according to Fried criteria

CFS= clinical frailty scale, AFN= acute frailty network frailty criteria, DFI= derby frailty index EFS= Edmonton frailty scale, DI= deficit index, Fried= Fried criteria, 5MWT= 5 meter walk test, TUGT= timed get up and go test, PPV= positive predictive value, NPV= negative predictive value.

7.4.8 Inter-operator agreement of CFS

There was a close agreement between the two operators' judgement on the degree of frailty in a random sample of patients (N=23) using the CFS, with a Kappa coefficient (K) of 0.72 (95% CI: 0.51-0.93, P<0.001).

7.4.9 Time needed to complete frailty screening vs assessment

Frailty screening on average took no more than 1 minute to complete, whereas frailty assessment on average took 15 minutes to complete, depending on the mobility of patients.

7.5 Discussion

The main finding of this study is that frailty was very common amongst outpatients with CHF, with a prevalence of 30-52% depending on the tool used. Our findings are similar to those from 2 recent meta-analyses. Jha and colleagues studied 2697 patients with CHF and reported a prevalence of 18-54% (172). Frailty was assessed by several tools including the Fried criteria, comprehensive geriatric assessment, DI, frailty staging system and modified frailty scale. Wang and colleagues studied 2411 patients with CHF and reported a prevalence of 25-76% (156). Frailty was assessed by several tools including the Fried criteria, frailty staging system and gait speed. There was a substantial variation in the prevalence of frailty reported in these meta-analyses, probably due to heterogeneity of the populations studied. Our results are a more accurate reflection of the true prevalence of frailty in patients with CHF, as frailty was evaluated using 6 different tools in the same cohort of patients.

Frailty was more common in patients with HeFNEF than in patients with HeFREF. Patients with HeFNEF were older and had a greater burden of non-cardiac co-morbidities, themselves associated with a reduced functional status and an increased risk of hospitalisation (173). AF becomes more common with age, and is particularly common in patients with HeFNEF. It is itself associated with the development and progression of frailty (174).

The control group included patients with co-morbidities such as coronary artery disease, diabetes and HTN, which substantially increase the risk of developing HF; however, the prevalence of frailty in this population was very low. This might suggest that there is a complex interplay and pathophysiological overlap between HF and frailty.

This study is the first to compare simple frailty screening tools with more comprehensive assessment tools in patients with CHF. Whilst there was substantial overlap between patients identified as frail by each tool, the overlap was not absolute. Although different tools take into account different factors contributing to frailty, these factors are often correlated with one another. For example, patients with a higher co-morbidity burden (as evaluated by tools looking at multi-dimensional frailty) are at higher risk of physical deconditioning (as evaluated by tools looking at physical frailty). Furthermore, although the Fried criteria and the DI assess frailty from 2 different perspectives, they were strongly correlated with each other. In fact, all the tools that I have studied in this chapter, were at least moderately correlated with each other, suggesting that although they consist of different components and none is on its own definitive, the tools reflect a common underlying phenotype.

Different tools have their own strengths and weaknesses. The Fried criteria objectively measures physical functioning, but other domains, particularly cognition, are not considered. The DI covers multiple domains including physical functioning and co-morbidities, and is thus a more comprehensive tool than the Fried criteria. The EFS, similar to the DI, also examines multiple domains including cognition, social support, medication, nutrition and mood; it also includes a straightforward physical performance measure: TUGT. Frailty assessments require significant time to perform (on average 15 minutes depending on the mobility of patients), which is not ideal in busy clinical settings.

Screening tools are much easier to use. They do not require physical tests and can be completed within a minute. Amongst the screening tools, CFS has the highest sensitivity and specificity with the lowest misclassification rate. In fact, CFS was as effective as lengthy assessment tools in detecting frailty, and might be appealing for use in clinical practice. CFS has a subjective component, but inter-operator agreement was found to be good.

Worsening results on physical performance measures such as handgrip strength and gait speed predict increasing morbidity and mortality (89, 90). Our results showed that single physical tests have higher sensitivities but lower specificities and higher misclassification rates compared to frailty screening or assessment tools. Further studies are needed to clarify whether single physical tests or simple frailty screening tools have comparable prognostic significance to more comprehensive frailty assessments.

7.6 Study limitations

Firstly, this is a single-centre study with limited sample size; external validation of our results from other populations is needed. This study is, however, the largest study which compares the agreement and classification performance of several commonly used frailty screening and assessment tools in consecutive, unselected, patients with CHF.

Secondly, I have only studied 6 of the most commonly used frailty tools in literature. A large number of frailty screening and assessment tools have been proposed and identified patients at risk of adverse outcomes in other clinical scenarios (43).

Thirdly, I have only included patients with a diagnosis of dementia if they had capacity to consent for the study. I did not study the role of frailty in patients with dementia so severe as to be considered lacking in capacity.

Lastly, this study only focused on investigating the prevalence of frailty using different tools. Further studies are needed to explore the prognostic significance of these tools and establish which tool(s) is/are the best to use in patients with CHF.

7.7 Conclusion

Frailty is common in patients with CHF. CFS is a short and easy to use frailty screening tool, which has comparable performance to lengthy assessments tools in identifying frailty. Further work is required to study their prognostic value in patients with CHF. The next chapter will explore whether single physical tests or simple frailty screening tools have comparable prognostic significance to more comprehensive frailty assessments.

Chapter 8 Prognostic Significance of Frailty Tools in Patients with Chronic Heart Failure

8.1 Chapter summary

Background: Frailty is common in patients with CHF and is associated with adverse outcomes, but it is uncertain how frailty should best be measured.

Objectives: To compare the prognostic significance of several commonly used frailty tools in ambulatory patients with CHF.

Methods: I evaluated frailty, simultaneously, using 3 screening tools (Clinical frailty scale (CFS); Derby frailty index (DFI); and Acute Frailty Network (AFN) criteria), 3 assessment tools (Fried criteria; Edmonton frailty scale (EFS); and Deficit index (DI)) and 3 physical tests (handgrip strength, timed get up and go test (TUGT); and five-metre walk test (5MWT)) in consecutive patients with CHF attending a routine follow-up visit.

Results: I studied 467 patients (67% male, median age 76 (IQR: 69-82) years, median NT-proBNP 1156 (IQR: 469-2463) ng/L). During a median follow-up of 554 (IQR: 511-629) days, 82 (18%) patients died and 201 (43%) patients were either hospitalised or died.

In models corrected for age, NYHA class, log [NT-proBNP], Charlson score, Hb, eGFR and AF, all frailty tools, with the exception of handgrip strength, AFN and DFI, were significant predictors of all-cause mortality.

A base model for predicting mortality including NYHA class, log [NT-proBNP] and AF, had a Harrell's C-statistic of 0.71. Amongst screening tools: CFS (C-statistic 0.75); amongst assessment tools: DI (C-statistic 0.76) and amongst physical tests: 5MWT (C-statistic 0.76), increased model performance most compared to base model ($P<0.05$ for all).

Conclusion: Frailty is strongly associated with increased mortality in ambulatory patients with CHF. CFS and 5MWT are simple tools that provide comparable prognostic information to assessment tools taking longer to perform.

8.2 Introduction

HF is increasingly common as the population ages. It is a leading cause of hospitalisation associated with poor outcomes and high medical costs (175). Frailty is a medical syndrome characterised by diminished strength and reduced physiological function that increases an individual's vulnerability for developing increased dependency and/or death (30). Up to 70% of patients with HF fulfil diagnostic criteria for frailty (176). This has important consequences on morbidity and mortality (5).

Despite an increasing awareness of frailty in patients with HF, there is no consensus on how frailty should be measured. Many frailty tools have been proposed (177), and each has its own advantages and disadvantages. Screening tools are easy to use and might be more suitable in a busy clinical setting. Assessment tools are time-consuming, but might give a more comprehensive frailty evaluation. Physical tests also require a large amount of time and resources, and might be challenging to perform in patients with reduced mobility. Whether different tools have different prognostic value is unknown.

In Chapter 7, I have studied in detail the agreement and classification performance of several commonly used frailty tools. In this chapter, I will compare the prognostic significance of these tools in a cohort of well-characterised ambulatory patients with CHF.

8.3 Methods

8.3.1 Study population

I prospectively recruited 467 consecutive ambulatory patients with CHF who attended our community HF clinic at Castle Hill Hospital, Hull, UK, between September 2016 and March 2017. All patients had a pre-existing (>1 year) clinical diagnosis of CHF. Details of the study population has been described in the 'methods' section of Chapter 7.

8.3.2 Frailty evaluation

I evaluated frailty in patients with CHF using the following tools:

- Screening tools:
    1. Derby frailty index (DFI)
    2. Acute frailty network criteria (AFN)
    3. Clinical frailty scale (CFS)
- Assessment tools
    1. Fried criteria
    2. Edmonton frailty scale (EFS)
    3. Deficit index (DI)
- Physical tests:
    1. Handgrip strength
    2. Timed get up and go test (TUGT)
    3. Five meter walk test (5MWT)

The entire frailty evaluation process took 1-1.5 hours per patient. A description of the frailty evaluation process can be found in the 'frailty evaluation' section of Chapter 4.

8.3.3 End points and follow up

I followed the patients until 1st of August 2018. All patients were followed for a minimum of 1 year. The primary end point was all-cause mortality and the secondary end point was the combination of all-cause hospitalisation and all-cause mortality. The handling of data regarding mortality and hospitalisation can be found in the 'end points and follow up section' in Chapter 4.

8.3.4 Statistical analysis

Routine statistical analyses have been detailed in Chapter 4.

I studied the prognostic significance of different frailty tools using several steps. Firstly, I performed univariable analysis with Cox proportional hazard regression to determine significant predictors of events. Then, I entered the clinical variables with $P<0.05$ in univariable analysis into multivariable models with each frailty tool both as a continuous and a binary variable. Next, I created a base model including NYHA (III/IV vs I/II), log [NT-proBNP] and cardiac rhythm (AF vs SR) for predicting mortality. I excluded age and co-morbidities (such as anaemia and renal dysfunction) from the model as some of the frailty tools take into account these variables. I added each of the frailty tools in turn to the base model and used Harrell's C-statistic to evaluate model discrimination in survival analysis. Furthermore, I constructed Kaplan-Meier curves to present time-to-event data. Finally, I performed further analyses to study the relationship between the degree of frailty and outcome. I used the frailty tool from each category (screening tools, assessment tools and physical tests) which best predicted all-cause mortality (highest χ^2).

To evaluate the length of stay during hospitalisation, I only included patients with ≥1 hospitalisation and hospitalisations resulting in death were excluded.

8.4 Results

8.4.1 Baseline characteristics

A total of 467 consecutive ambulatory patients with CHF was studied. The baseline characteristics of CHF patients have been shown in Table 7.1. Table 8.1 shows the baseline characteristics of CHF patients who survived at 1 year follow up vs those who did not. Compared to patients who were alive at 1 year, those who died were older, had more severe symptoms and were more likely to be frail at baseline. They also had higher NT-proBNP, lower BMI, more co-morbidities and were less likely to be treated with an ACEi/ARB but more likely to be treated with a loop diuretic and digoxin (Table 8.1).

Table 8.1: Baseline characteristics of CHF patients (died by 1 year vs alive at 1 year).

	Died by 1 year N=56	**Alive at 1 year** N=411	**P**
Demographics			
Age (years)	82 (77-87)	75 (68-82)	<0.001
Sex (male), n (%)	38 (68)	275 (67)	0.88
BP systolic (mmHg)	136 (127-160)	140 (125-162)	0.89
BP diastolic (mmHg)	74 (66-83)	75 (66-83)	0.63
HR (bpm)	70 (60-82)	70 (60-80)	0.84
Rhythm (AF), n (%)	37 (66)	178 (43)	0.001
Height (m)	1.69 (1.60-1.75)	1.68 (1.61-1.75)	0.68
Weight (kg)	77 (66-89)	83 (69-100)	0.009
BMI (kg/m^2)	27 (23-30)	29 (26-33)	0.004
NYHA III-IV, n (%)	24 (43)	79 (19)	<0.001
HeFREF, n (%)	35 (63)	256 (62)	0.37
LVEF (%)	44 (34-51)	45 (35-54)	0.31
Co-morbidities			
MI, n (%)	21 (38)	177 (43)	0.43
PVD, n (%)	14 (25)	58 (14)	0.03
HTN, n (%)	37 (66)	276 (67)	0.87
CVD, n (%)	13 (23)	58 (14)	0.08
Diabetes Mellitus, n (%)	22 (39)	141 (34)	0.46
Dementia, n (%)	20 (36)	28 (7)	<0.001
COPD, n (%)	23 (41)	117 (29)	0.05
Depression, n (%)	16 (29)	77 (19)	0.08
Anaemia, n (%)	44 (79)	174 (42)	<0.001
Falls, n (%)	33 (59)	140 (34)	<0.001
Urinary incontinence, n (%)	8 (14)	25 (6)	0.03
Charlson Score	10 (9-12)	8 (6-10)	<0.001

Table 8.1 (continued): Baseline characteristics of CHF patients (died by 1 year vs alive at 1 year).

	Died by 1 year N=56	**Alive at 1 year** N=411	**P**
Medications			
ACEi/ARB, n (%)	35 (63)	354 (86)	<0.001
BB, n (%)	44 (79)	348 (85)	0.24
MRA, n (%)	23 (41)	191 (47)	0.45
Loop diuretics, n (%)	49 (88)	298 (73)	0.02
Thiazide diuretics, n (%)	2 (4)	15 (4)	0.98
Digoxin, n (%)	18 (32)	82 (20)	0.04
≥5 medications, n (%)	53 (95)	351 (85)	0.06
Blood tests			
NT-proBNP (ng/L)	2507 (1434-5825)	1001 (428-2150)	<0.001
Hb (g/dL)	11.7 (10.6-13.1)	13.2 (12.0-14.3)	<0.001
Sodium (mmol/L)	136 (133-138)	137 (135-138)	0.04
Potassium (mmol/L)	4.4 (4.1-4.7)	4.4 (4.2-4.7)	0.40
eGFR (ml/min/1.73 m^2)	39 (28-58)	58 (42-74)	<0.001
Frailty tools			
DFI (frail), n (%)	43 (77)	181 (44)	<0.001
AFN (frail), n (%)	45 (80)	172 (42)	<0.001
CFS (frail), n (%)	46 (82)	160 (39)	<0.001
TUGT (frail), n (%)	53 (95)	268 (65)	<0.001
Grip strength (frail), n (%)	51 (91)	241 (59)	<0.001
5MWT (frail), n (%)	53 (95)	241 (59)	<0.001
Fried (frail), n (%)	49 (88)	195 (47)	<0.001
DI (frail), n (%)	41 (73)	124 (30)	<0.001
EFS (frail), n (%)	35 (63)	105 (26)	<0.001

HR= heart rate, AF= atrial fibrillation, BP= blood pressure, NYHA= New York Heart Association, HeFREF= heart failure with reduced ejection fraction, LVEF= left ventricular ejection fraction, BMI= body mass index, MI= myocardial infarction, PVD= peripheral vascular disease, HTN= hypertension, CVD= cerebrovascular disease, COPD= chronic obstructive pulmonary disease, BB= beta-blocker, ACEi= angiotensin converting enzyme inhibitor, ARB= angiotensin receptor blocker, MRA= mineralocorticoid receptor antagonist, NT-proBNP= N-terminal pro-B-type natriuretic peptide, Hb= haemoglobin, eGFR = estimated glomerular filtration rate, DFI= Derby frailty index, AFN= Acute frailty network frailty criteria, CFS= Clinical frailty scale, TUGT= Timed get up and go test, 5MWT= 5 meter walk test, DI= Deficit index, EFS= Edmonton frailty scale.

8.4.2 Relation between frailty and mortality

During a median follow-up of 554 days (IQR: 511-629 days), 18% of patients died. The influence of frailty measures considered as univariable predictors of mortality is shown in Table 8.2a with Table 8.2b showing the results for other clinical variables. The presence of frailty, as determined by any tool, was associated with an increased risk of mortality.

Table 8.2a: Univariable analysis of frailty tools predicting all-cause mortality.

Worse outcome per unitary increase		**HR (95%CI)**	**χ^2**
Physical tests	5MWT*	1.14 (1.09-1.20)	31.2
	5MWT (Frail vs non-frail)	6.17 (2.98-12.80)	23.9
	TUGT*	1.08 (1.05-1.11)	29.8
	TUGT (Frail vs non-frail)	6.46 (2.81-14.83)	19.3
	Grip strength **	1.05 (1.03-1.07)	22.0
	Grip strength (Frail vs non-frail)	3.88 (2.10-7.15)	18.8
Screening	CFS	2.30 (1.88-2.80)	66.6
	CFS (Frail vs non-frail)	4.27 (2.60-7.01)	32.8
	AFN (Frail vs non-frail)	4.02 (2.43-6.65)	29.2
	DFI (Frail vs non-frail)	2.59 (1.63-4.13)	16.1
Assessment	Fried criteria	1.79 (1.51-2.13)	44.4
	Fried criteria (Frail vs non-frail)	4.66 (2.66-8.15)	29.0
	DI (per 0.01 increase)	1.06 (1.05-1.08)	75.4
	DI (Frail vs non-frail)	4.44 (2.67-7.14)	37.6
	EFS	1.32 (1.23-1.42)	58.1
	EFS (Frail vs non-frail)	3.43 (2.22-5.31)	30.7

*53 patients were excluded as they were unable to perform 5m walk test or TUGT. ** Per unitary decrease

All P<0.001.

HR = hazard ratio, CI= confidence interval, χ^2= chi-square, 5 MWT= 5-meter walk test, TUGT= Timed get up and go test, CFS= Clinical frailty scale, AFN= Acute frailty network criteria, DFI= Derby frailty index, DI= Deficit index, EFS= Edmonton frailty scale.

Table 8.2b: Univariable analysis of clinical factors predicting all-cause mortality.

Worse outcome per unitary increase	**HR (95% CI)**	**χ^2**	**P**
Age (years)	1.07 (1.04-1.09)	24.0	<0.001
Sex (male vs female)	1.26 (0.78-2.05)	0.9	0.34
BMI (kg/m^2)	0.95 (0.91-0.98)	8.2	0.004
Rhythm (AF vs SR)	1.98 (1.27-3.09)	9.1	0.003
NYHA (III/IV vs I/II)	2.89 (1.86-4.48)	22.3	<0.001
LVI (≥Mod vs < mod)	1.05 (0.68-1.62)	0.1	0.82
Charlson score	1.36 (1.25-1.48)	50.3	<0.001
MI (Y vs N)	1.15 (0.75-1.78)	0.4	0.52
PVD (Y vs N)	1.62 (0.96-2.74)	3.3	0.07
HTN (Y vs N)	0.94 (0.59-1.48)	0.1	0.77
CVD (Y vs N)	1.86 (1.13-3.08)	5.8	0.02
Diabetes (Y vs N)	1.34 (0.86-2.08)	1.7	0.19
Dementia (Y vs N)	4.37 (2.69-7.07)	35.8	<0.001
COPD (Y vs N)	1.83 (1.18-2.84)	7.4	0.01
Depression (Y vs N)	1.34 (0.81-2.21)	1.3	0.26
Anaemia (Y vs N)	4.03 (2.43-6.68)	29.4	<0.001
Recurrent falls (Y vs N)	2.01 (1.30-3.10)	9.9	0.002
Log [NT-proBNP] (ng/L)	5.88 (3.56-9.70)	48.0	<0.001
Hb (g/L)	0.96 (0.95-0.98)	28.2	<0.001
Sodium (mmol/L)	0.95 (0.89-1.01)	3.1	0.08
Potassium (mmol/L)	0.99 (0.61-1.61)	0.001	0.97
eGFR (mL/min per 1.73 m^2)	0.97 (0.96-0.98)	25.2	<0.001

HR = hazard ratio, CI= confidence interval, χ^2= chi-square, BMI =body mass index, AF= atrial fibrillation, SR= sinus rhythm, NYHA= New York Heart Association, LVI= left ventricular impairment, MI= myocardial infarction, PVD= peripheral vascular disease, HTN= hypertension, CVD= cerebrovascular disease, COPD= chronic obstructive pulmonary disease, NT-proBNP= N-terminal pro-B-type natriuretic peptide, Hb= haemoglobin, eGFR = estimated glomerular filtration rate, Y=yes, N=no.

Clinical variables included in multivariable analyses for predicting mortality are shown in Table 8.3a. All frailty tools, with the exception of handgrip strength, AFN, DFI and EFS (when used as a binary variable), were significant predictors of all-cause mortality when evaluated individually in multivariable analysis (Table 8.3b).

Table 8.3a: Clinical variables included in multivariable analyses for predicting all-cause mortality. (using CFS as an example).

Worse outcome per unitary increase	**HR (95%CI)**	**χ^2**	**P**
Age (years)	1.00 (0.96-1.03)	0.16	0.69
BMI (kg/m^2)	0.97 (0.93-1.01)	1.84	0.18
Rhythm (AF vs SR)	1.24 (0.76-2.03)	0.75	0.39
NYHA (III/IV vs I/II)	1.01 (0.61-1.68)	0.002	0.96
Charlson Score	1.09 (0.96-1.24)	1.93	0.17
Log [NT-proBNP]	2.35 (1.31-4.24)	8.14	0.004
Hb (g/L)	1.00 (0.98-1.01)	0.75	0.39
eGFR (mL/min per 1.73 m^2)	1.00 (0.98-1.01)	1.80	0.18
CFS	**1.76 (1.36-2.27)**	**18.87**	**<0.001**

HR = hazard ratio, CI= confidence interval, χ^2= chi-square, BMI= body mass index, AF= atrial fibrillation, SR= sinus rhythm, NYHA= New York Heart Association, NT-proBNP= N-terminal pro-B-type natriuretic peptide, Hb= haemoglobin, eGFR = estimated glomerular filtration rate, CFS = clinical frailty scale.

A base model including NYHA (III/IV vs I/II), log [NT-proBNP] and cardiac rhythm (AF vs SR) for predicting mortality achieved a Harrell's C-statistic of 0.71 (Table 8.4). Each frailty tool, when added individually, improved performance of the base model. Amongst screening tools: CFS (C-statistic 0.75); amongst assessment tools: DI (C-statistic 0.76); and amongst physical tests: 5MWT (C-statistic 0.76) increased model performance most compared with the base model (all P<0.05).

Figure 8.1 shows the Kaplan Meier curves illustrating the relation between frailty and all-cause mortality. Patients who were frail according to the CFS, DI and 5MWT had a 6 to 9 times greater mortality risk than those who were not frail.

Table 8.3b: Multivariable analysis of frailty tools predicting all-cause mortality. (Separate multivariable analysis was performed for each tool as both a binary and a continuous variable, with Table 8.3a showing the clinical variables included in multivariable analyses for predicting all-cause mortality)

Worse outcome per unitary increase		HR (95%CI)	χ^2	P
Physical tests	5MWT*	1.08 (1.01-1.15)	4.9	0.03
	5MWT (Frail vs non-frail)	2.97 (1.38-6.43)	7.7	0.006
	TUGT*	1.05 (1.01-1.09)	5.8	0.02
	TUGT (Frail vs non-frail)	2.62 (1.09-6.32)	4.6	0.03
	Grip strength **	1.01 (0.99-1.03)	0.7	0.40
	Grip strength (Frail vs non-frail)	1.66 (0.84-3.27)	2.1	0.15
Screening	CFS	1.76 (1.36-2.27)	18.9	<0.001
	CFS (Frail vs non-frail)	1.97 (1.12-3.46)	5.5	0.02
	AFN (Frail vs non-frail)	1.71 (0.91-3.20)	2.8	0.10
	DFI (Frail vs non-frail)	0.79 (0.40-1.56)	0.5	0.49
Assessment	Fried criteria	1.35 (1.10-1.66)	8.4	0.004
	Fried criteria (Frail vs non-frail)	2.09 (1.13-3.89)	5.4	0.02
	DI (per 0.01 increase)	1.05 (1.02-1.07)	15.8	<0.001
	DI (Frail vs non-frail)	2.30 (1.32-4.03)	8.5	0.003
	EFS	1.18 (1.08-1.30)	12.6	<0.001
	EFS (Frail vs non-frail)	1.58 (0.95-2.65)	3.1	0.08

Variables in multivariable analysis predicting all-cause mortality included: Age, BMI, cardiac rhythm (AF vs SR), NYHA (III/IV vs I/II), Charlson score, log[NT-proBNP], Hb, eGFR.

*53 patients were excluded as they were unable to perform 5MWT or TUGT.
** Per unitary decrease.

5MWT= 5-meter walk test, TUGT= Timed get up and go test, CFS= Clinical frailty scale, AFN= Acute frailty network criteria, DFI= Derby frailty index, DI= Deficit index, EFS= Edmonton frailty scale.

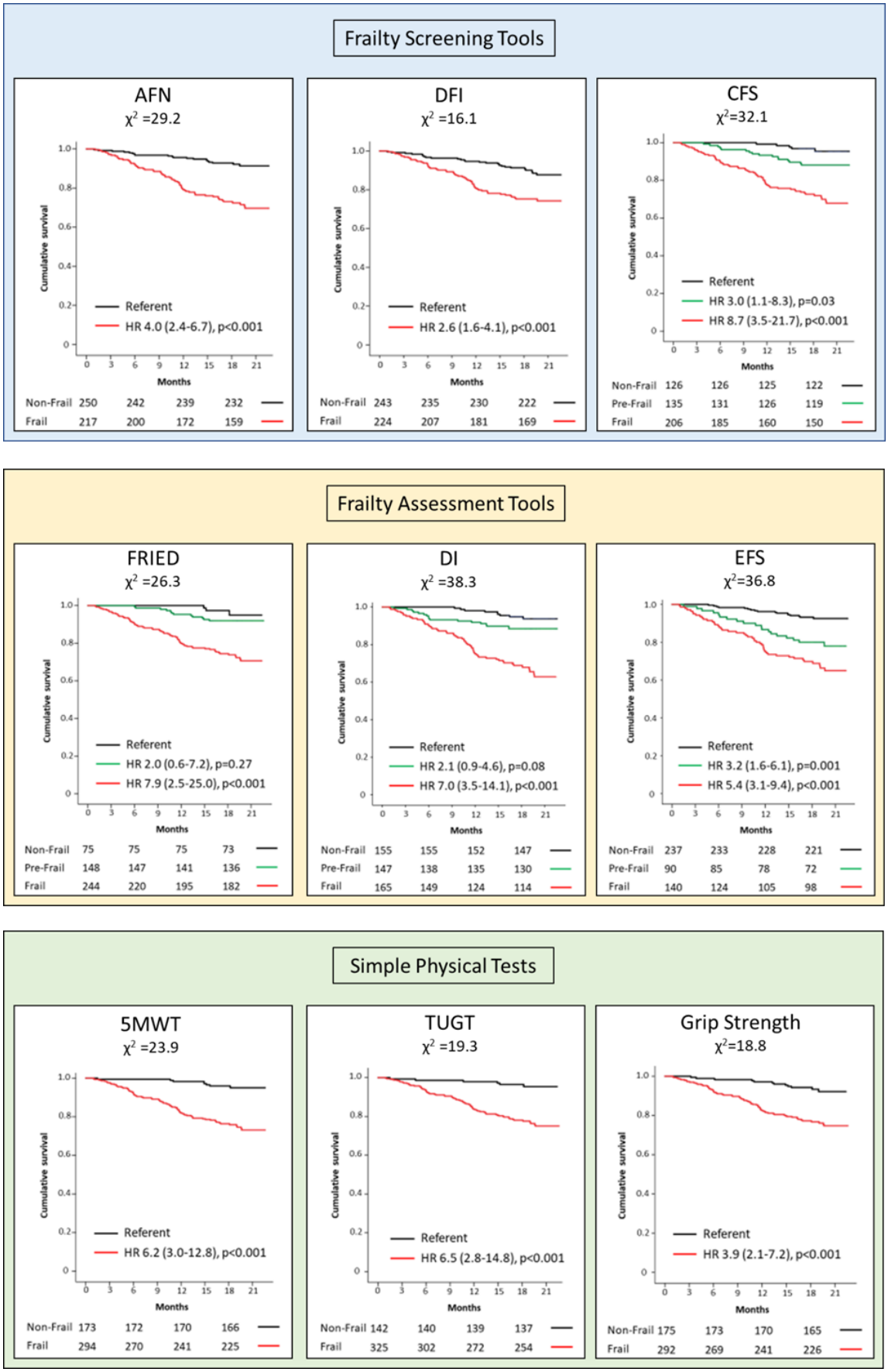
Table 8.4: Addition of frailty tools and its impact on performance of base model in predicting all-cause mortality.

Model	Harrell's C-statistics (95% CI)	Difference
Base model*	0.71 (0.66-0.77)	Compared to base model (t-statistic, P)
Screening tools		
Base* + CFS	0.75 (0.70-0.80)	t = 2.13, P = 0.03
Base* + AFN	0.74 (0.70-0.80)	t = 2.30, P = 0.02
Base* + DFI	0.73 (0.68-0.79)	t = 1.94, P = 0.05
Assessment tools		
Base* + Fried criteria	0.75 (0.70-0.80)	t = 2.30, P = 0.02
Base* + DI	0.76 (0.71-0.81)	t =2.24, P = 0.03
Base* + EFS	0.74 (0.69-0.79)	t =1.70, P = 0.09
Single tests		
Base* + 5MWT	0.76 (0.71-0.81)	t = 2.81, P = 0.01
Base* + TUGT	0.75 (0.69-0.80)	t = 2.33, P = 0.02
Base* + Grip strength	0.75 (0.69-0.79)	t = 2.15, P = 0.03

*Base model: NYHA (III/IV vs I/II), log [NT-proBNP], cardiac Rhythm (AF vs SR)

AF= atrial fibrillation, SR= sinus rhythm, NYHA= New York Heart Association, NT-proBNP= N-terminal pro-B-type natriuretic peptide, CFS = clinical frailty scale, DFI= Derby frailty index, AFN= Acute frailty network criteria, DI= Deficit index, EFS= Edmonton frailty scale, 5MWT 5 meter walk test, TUGT= Timed get up and go test, CI = confidence interval.

Figure 8.1: Kaplan Meier curves illustrating the relation between frailty tools and all-cause mortality.
(Top panel: screening tools; middle panel: assessment tools; bottom panel: physical tests)



The 3-month, 6-month and 12-month mortality according to frailty categories are shown in Tables 8.5a-c. Worsening frailty was associated with higher mortality rates. Severely frail patients had a much higher 1-year mortality rate (33-74%) than non-frail (1-2%) or pre-frail patients (2-13%).

Table 8.5a: 3-month, 6-month and 12-month mortality by categories of CFS. (Expressed as mortality rate (%), number of deaths)

	CFS					P
	Non-frail 1-3 (N=126)	Pre-frail 4 (N=135)	Mildly frail 5 (N=118)	Moderately frail 6 (N=69)	Severely frail ≥7 (N=19)	
3 month	0	0	2% (N=2)	4% (N=3)	16% (N=3)	<0.001
6 month	0	3% (N=4)	7% (N=8)	12% (N=8)	26% (N=5)	<0.001
12 month	1% (N=1)	7% (N=9)	13% (N=15)	25% (N=17)	74% (N=14)	<0.001

Table 8.5b: 3-month, 6-month and 12-month mortality by categories of DI. (Expressed as mortality rate (%), number of deaths)

	DI					P
	Non-frail 0.06-0.17 (N=88)	Pre-frail 0.18-0.23 (N=98)	Mildly frail 0.24-0.31 (N=93)	Moderately frail 0.32-0.41 (N=94)	Severely frail 0.42-0.72 (N=94)	
3 month	0	0	0	2% (N=2)	6% (N=6)	0.002
6 month	0	1% (N=1)	7% (N=6)	5% (N=5)	14% (N=13)	<0.001
12 month	2% (N=2)	2% (N=2)	9% (N=8)	14% (N=13)	33% (N=31)	<0.001

Mortality Rate: <5% 5-10% 10-20% 20-50% >50%

Table 8.5c: 3-month, 6-month and 12-month mortality by categories of 5MWT.

(Expressed as mortality rate (%), number of deaths)

	5MWT (sec)					P
	Non-frail ≤ 7 (N=195)	Pre-frail 7-9.5 (N=125)	Mildly frail 10-14.5 (N=67)	Moderately frail 15-28 (N=27)	Severely frail unable to complete (N=53)	
3 month	1% (N=1)	0	0	7% (N=2)	9% (N=5)	<0.001
6 month	1% (N=2)	6% (N=7)	5% (N=3)	7% (N=2)	21% (N=11)	<0.001
12 month	2% (N=4)	13% (N=16)	13% (N=9)	19% (N=5)	42% (N=22)	<0.001

Mortality Rate: <5% 5-10% 10-20% 20-50% >50%

The cause of death data is shown in Table 8.6. Of patients who died, most died of cardiovascular causes (55%).

Table 8.6: Cause of death of CHF patients at 1 year. (Expressed as number of deaths, proportion of deaths due to a specific cause)

Cause of death	**CHF** N=467 No. of deaths = 56	Cause of death	**CHF** N=467 No. of deaths = 56
Cardiovascular	31 (55%)	Non-cardiovascular	25 (45%)
MI	6 (11%)	Infection	15 (27%)
HF	20 (35%)	Renal failure	1 (2%)
Arrhythmia	1 (2%)	Comorbidities	9 (16%)
CVD	4 (7%)	Malignancy	4 (7%)
		COPD	1 (2%)
		Dementia	3 (5%)
		Parkinson's disease	1 (2%)

MI= myocardial infarction, CVD= cerebrovascular disease, COPD= chronic obstructive pulmonary disease.

Of patients who died of cardiovascular causes, most died of progression of HF (65%). Of patients who died of non-cardiovascular causes, most died of infection (60%), followed by co-morbidities (36%), most commonly malignancy (16%). Frail patients were also more likely to die of acute cerebral or cardiac ischaemic events than non-frail patients (Table 8.7).

Table 8.7: Cause of death at 1 year in frail vs non-frail patients by CFS, DI and 5MWT. (Expressed as number of deaths, proportion of deaths due to a specific cause)

Cause of death	**CFS**		**DI**		**5MWT**	
	F N=206 Deaths: 46	**NF** N=261 Deaths: 10	**F** N=165 Deaths: 43	**NF** N=302 Deaths: 13	**F** N=294 Deaths: 53	**NF** N=173 Deaths: 3
Cardiovascular	26 (57%)	5 (50%)	22 (51%)	9 (70%)	31 (59%)	0
MI	6 (13%)	0	5 (12%)	1 (8%)	6 (11%)	0
HF	15 (33%)	5 (50%)	12 (28%)	8 (62%)	20 (38%)	0
Arrhythmia	1 (2%)	0	1 (2%)	0	1 (2%)	0
CVD	4 (9%)	0	4 (9%)	0	4 (8%)	0
Non-cardiovascular	20 (43%)	5 (50%)	21 (49%)	4 (30%)	22 (41%)	3 (100%)
Infection	12 (26%)	3 (30%)	13 (31%)	2 (15%)	12 (22%)	3 (100%)
Renal failure	1 (2%)	0	1 (2%)	0	1 (2%)	0
Co-morbidities	7 (15%)	2 (20%)	7 (16%)	2 (15%)	9 (17%)	0
Malignancy	2 (4%)	2 (20%)	2 (5%)	2 (15%)	4 (7%)	0
COPD	1 (2%)	0	1 (2%)	0	1 (2%)	0
Dementia	3 (7%)	0	3 (7%)	0	3 (6%)	0
Parkinson's	1 (2%)	0	1 (2%)	0	1 (2%)	0

MI= myocardial infarction, CVD= cerebrovascular disease, COPD= chronic obstructive pulmonary disease, CFS= Clinical frailty scale, DI= Deficit index, 5MWT= 5 meter walk test, F = frail, NF = non-frail.

8.4.3 Relation between frailty and combined hospitalisation and mortality

During follow up, 43% of patients were either hospitalised or died. The influence of frailty measures considered as univariable predictors of the combined outcome is shown in Table 8.8a with Table 8.8b showing the results for other clinical variables. The presence of frailty, as determined by any tool, was associated with an increased risk of the combined outcome.

Table 8.8a: Univariable analysis of frailty tools predicting combined outcome.

Worse outcome per unitary increase		HR (95%CI)	χ^2
Physical tests	5MWT*	1.15 (1.11-1.18)	62.9
	5MWT (Frail vs non-frail)	2.68 (1.92-3.75)	33.3
	TUGT*	1.07 (1.05-1.09)	53.2
	TUGT (Frail vs non-frail)	3.91 (2.60-5.87)	43.3
	Grip strength **	1.04 (1.03-1.05)	41.7
	Grip strength (Frail vs non-frail)	2.84 (2.03-3.98)	36.7
Screening	CFS	1.87 (1.65-2.12)	96.9
	CFS (Frail vs non-frail)	2.85 (2.14-3.80)	51.2
	AFN (Frail vs non-frail)	3.03 (2.27-4.07)	55.4
	DFI (Frail vs non-frail)	2.80 (2.09-3.75)	47.8
Assessment	Fried criteria	1.58 (1.43-1.74)	78.8
	Fried criteria (Frail vs non-frail)	3.03 (2.23-4.11)	50.3
	DI (per 0.01 increase)	1.05 (1.04-1.06)	108.2
	DI (Frail vs non-frail)	2.87 (2.18-3.80)	55.3
	EFS	1.27 (1.21-1.33)	105.3
	EFS (Frail vs non-frail)	3.02 (2.29-3.99)	60.3

All P<0.001. HR = hazard ratio, CI= confidence interval, χ^2= chi-square, 5 MWT= 5 meter walk test, TUGT= Timed get up and go test, CFS= Clinical frailty scale, AFN= Acute frailty network frailty criteria, DFI= Derby frailty index, DI= Deficit index, EFS= Edmonton frailty scale.

*53 patients were excluded as they were unable to perform 5m walk test or TUGT. ** Per unitary decrease

Table 8.8b: Univariable analysis of clinical factors predicting combined outcome.

Worse outcome per unitary increase	**HR (95% CI)**	**χ^2**	**P**
Age (years)	1.05 (1.03-1.06)	37.4	<0.001
Sex (male vs female)	1.03 (0.76-1.38)	0.03	0.87
BMI (kg/m^2)	0.97 (0.95-1.00)	5.6	0.02
Rhythm (AF vs SR)	1.26 (0.96-1.66)	2.7	0.10
NYHA (III/IV vs I/II)	2.90 (2.17-3.87)	51.6	<0.001
LVI (≥Mod vs < mod)	1.08 (0.82-1.42)	0.3	0.60
Charlson score	1.29 (1.22-1.36)	87.6	<0.001
MI (Y vs N)	1.02 (0.77-1.34)	0.01	0.91
PVD (Y vs N)	1.47 (1.04-2.08)	4.6	0.03
HTN (Y vs N)	0.91 (0.68-1.22)	0.4	0.53
CVD (Y vs N)	1.64 (1.16-2.31)	7.8	0.01
Diabetes (Y vs N)	1.31 (0.99-1.74)	3.6	0.06
Dementia (Y vs N)	3.41 (2.39-4.86)	45.5	<0.001
COPD (Y vs N)	1.71 (1.28-2.27)	13.4	<0.001
Depression (Y vs N)	1.32 (0.94-1.84)	2.62	0.11
Anaemia (Y vs N)	2.65 (1.99-3.54)	43.9	<0.001
Recurrent falls (Y vs N)	2.16 (1.64-2.85)	29.6	<0.001
Log [NT-proBNP] (ng/L)	3.08 (2.26-4.20)	50.7	<0.001
Hb (g/L)	0.97 (0.96-0.98)	53.0	<0.001
Sodium (mmol/L)	0.96 (0.93-1.00)	3.06	0.08
Potassium (mmol/L)	0.94 (0.67-1.30)	0.16	0.69
eGFR (mL/min per 1.73 m^2)	0.98 (0.97-0.98)	38.4	<0.001

HR = hazard ratio, CI= confidence interval, χ^2= chi-square, BMI =body mass index, AF= atrial fibrillation, SR= sinus rhythm, NYHA= New York Heart Association, LVI= left ventricular impairment, MI= myocardial infarction, PVD= peripheral vascular disease, HTN= hypertension, CVD= cerebrovascular disease, COPD= chronic obstructive pulmonary disease, NT-proBNP= N-terminal pro-B-type natriuretic peptide, Hb= haemoglobin, eGFR = estimated glomerular filtration rate, Y=yes, N=no.

Clinical variables included in multivariable analyses for predicting the combined outcome are shown in Table 8.9a. All frailty tools, with the exception of handgrip strength and 5MWT (when used as a binary variable), were significant predictors of the combined outcome when evaluated individually in multivariable analysis (Table 8.9b).

Table 8.9a: Clinical variables included in multivariable analyses for predicting combined outcome. (using CFS as an example)

Worse outcome per unitary increase	**HR (95%CI)**	**χ^2**	**P**
Age (years)	1.00 (0.98-1.02)	0.04	0.83
BMI (kg/m^2)	0.98 (0.96-1.01)	1.6	0.20
NYHA (III/IV vs I/II)	1.43 (1.02-1.98)	4.4	0.04
Charlson Score	1.13 (1.04-1.22)	9.1	0.003
Log [NT-proBNP]	1.56 (1.10-2.21)	6.3	0.01
Hb (g/L)	0.98 (0.98-0.99)	9.6	0.002
eGFR (mL/min per 1.73 m^2)	1.00 (0.99-1.01)	0.01	0.92
CFS	**1.35 (1.15-1.58)**	**13.7**	**<0.001**

Cardiac rhythm (AF vs SR) is not included in multivariable analysis predicting combined outcome as it is not a significant predictor of combined outcome in univariable analysis.

HR = hazard ratio, CI= confidence interval, χ^2= chi-square, BMI= body mass index, AF= atrial fibrillation, SR= sinus rhythm, NYHA= New York Heart Association, NT-proBNP= N-terminal pro-B-type natriuretic peptide, Hb= haemoglobin, eGFR = estimated glomerular filtration rate, CFS = clinical frailty scale.

Figure 8.2 shows the Kaplan Meier curves illustrating the relation between frailty and the combined outcome. Patients who were frail according to the CFS, DI and 5MWT had a 3-6 times greater risk of the combined outcome than those who were not frail.

The 3-month, 6-month and 12-month combined event rates according to frailty categories are shown in Tables 8.10a-c. Worsening frailty was associated with higher combined event rates. Severely frail patients had a much higher 3-month combined event rate (33-47%) than non-frail (1-5%) or pre-frail patients (1-13%). A similar trend was seen in 6-month and 12-month combined event rates.

Table 8.9b: Multivariable analysis of frailty tools predicting combined outcome. (Separate multivariable analysis was performed for each tool as both a binary and a continuous variable, with Table 8.9a showing the clinical variables included in multivariable analyses for predicting the combined outcome)

Worse outcome per unitary increase		**HR (95%CI)**	**χ^2**	**P**
Physical tests	5MWT*	1.07 (1.03-1.12)	10.9	0.001
	5MWT (Frail vs non-frail)	1.43 (0.99-2.07)	3.5	0.06
	TUGT*	1.04 (1.01-1.06)	9.3	0.002
	TUGT (Frail vs non-frail)	2.07 (1.34-3.21)	10.7	0.001
	Grip strength **	1.01 (0.99-1.02)	1.2	0.28
	Grip strength (Frail vs non-frail)	1.40 (0.96-2.06)	3.0	0.08
Screening	CFS	1.35 (1.15-1.58)	13.7	<0.001
	CFS (Frail vs non-frail)	1.38 (0.98-1.93)	3.5	0.06
	AFN (Frail vs non-frail)	1.57 (1.08-2.30)	5.5	0.02
	DFI (Frail vs non-frail)	1.63 (1.06-2.52)	4.9	0.03
Assessment	Fried criteria	1.23 (1.09-1.39)	11.4	0.001
	Fried criteria (Frail vs non-frail)	1.56 (1.10-2.20)	6.2	0.01
	DI (per 0.01 increase)	1.02 (1.01-1.04)	9.3	0.002
	DI (Frail vs non-frail)	1.40 (0.99-1.98)	3.7	0.05
	EFS	1.15 (1.08-1.21)	22.1	<0.001
	EFS (Frail vs non-frail)	1.54 (1.11-2.12)	6.7	0.01

Variables in multivariable analysis predicting combined outcome included: Age, BMI, NYHA (III/IV vs I/II), Charlson score, log[NT-proBNP], Hb, eGFR (AF vs sinus rhythm is not included as it is not a significant predictor of combined outcome in univariable analysis).

*53 patients were excluded as they were unable to perform 5m walk test or TUGT.
** Per unitary decrease.

5 MWT= 5 meter walk test, TUGT= Timed get up and go test, CFS= Clinical frailty scale, AFN= Acute frailty network frailty criteria, DFI= Derby frailty index, DI= Deficit index, EFS= Edmonton frailty scale.

Figure 8.2: Kaplan Meier curves illustrating the relation between frailty tools and combined outcome. (Top panel: screening tools; middle panel: assessment tools; bottom panel: physical tests)

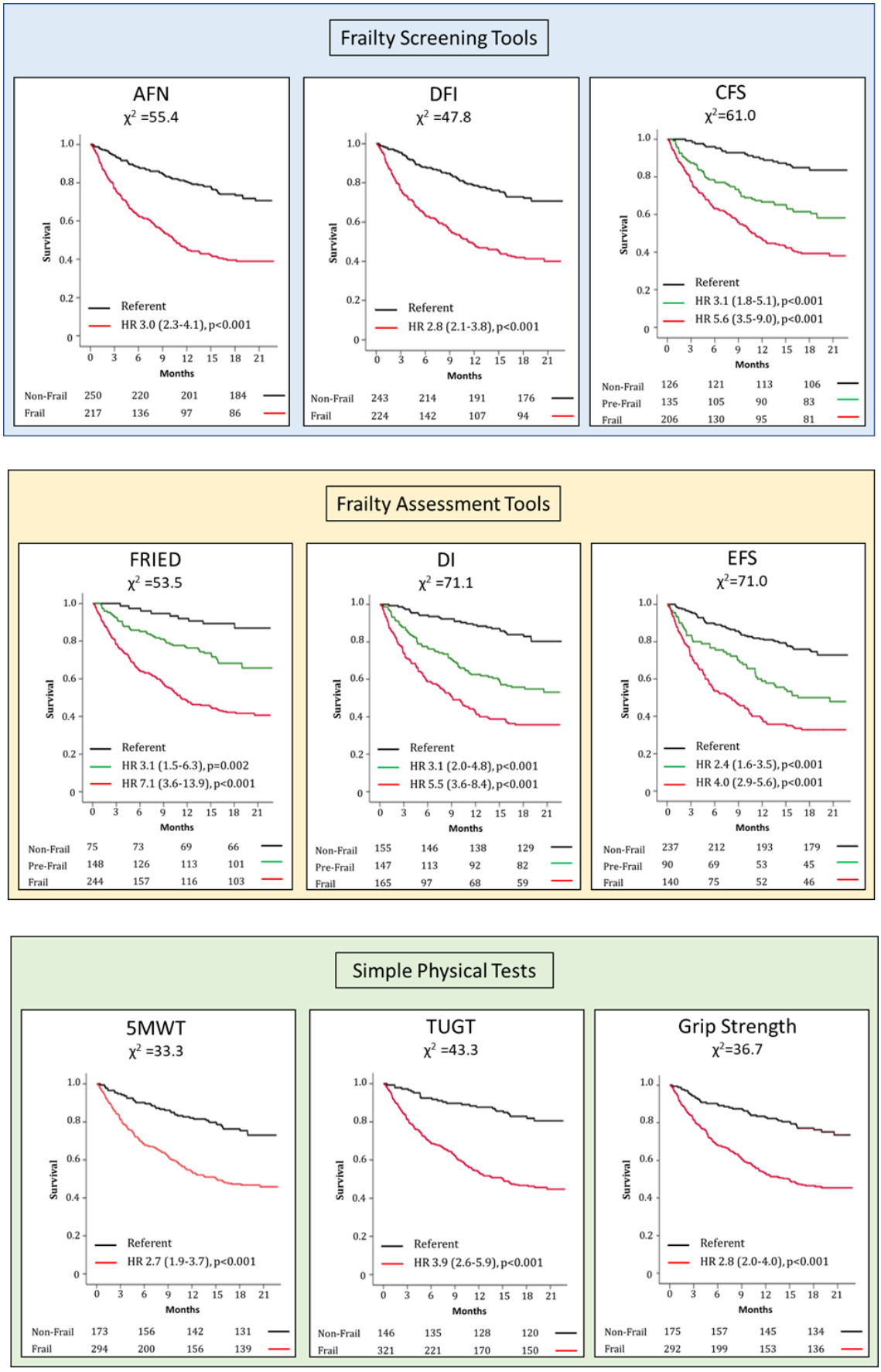


Table 8.10a: 3-month, 6-month and 12-month combined event rates by categories of CFS. (Expressed as combined outcome rate (%), number of events).

	CFS					P
	Non-frail 1-3 (N=126)	Pre-frail 4 (N=135)	Mildly frail 5 (N=118)	Moderately frail 6 (N=69)	Severely frail ≥7 (N=19)	
3 month	1% (N=1)	13% (N=17)	12% (N=14)	33% (N=23)	47% (N=9)	<0.001
6 month	5% (N=6)	23% (N=31)	22% (N=26)	51% (N=35)	79% (N=15)	<0.001
12 month	10% (N=13)	33% (N=45)	40% (N=47)	67% (N=46)	95% (N=18)	<0.001

Table 8.10b: 3-month, 6-month and 12-month combined event rates by categories of DI. (Expressed as combined outcome rate (%), number of events)

	DI					P
	Non-frail 0.06-0.17 (N=88)	Pre-frail 0.18-0.23 (N=98)	Mildly frail 0.24-0.31 (N=93)	Moderately frail 0.32-0.41 (N=94)	Severely frail 0.42-0.72 (N=94)	
3 month	2% (N=2)	1% (N=1)	15% (N=14)	17% (N=16)	33% (N=31)	<0.001
6 month	7% (N=6)	8% (N=8)	24% (N=22)	30% (N=28)	52% (N=49)	<0.001
12 month	10% (N=9)	16% (N=16)	37% (N=34)	49% (N=46)	68% (N=64)	<0.001

Combined event rate: <5% 5-10% 10-20% 20-50% >50%

Table 8.10c: 3-month, 6-month and 12-month combined event rates by categories of 5MWT. (Expressed as combined outcome rate (%), number of events)

	5MWT (sec)					P
	Non-frail ≤ 7 (N=195)	Pre-frail 7-9.5 (N=125)	Mildly frail 10-14.5 (N=67)	Moderately frail 15-28 (N=27)	Severely frail unable to complete (N=53)	
3 month	5% (N=10)	12% (N=15)	16% (N=11)	30% (N=8)	38% (N=20)	<0.001
6 month	11% (N=21)	22% (N=27)	27% (N=18)	52% (N=14)	62% (N=33)	<0.001
12 month	18% (N=35)	36% (N=45)	43% (N=29)	74% (N=20)	76% (N=40)	<0.001

Combined event rate: <5% 5-10% 10-20% 20-50% >50%

8.4.4 Relation between frailty and hospitalisation

32% of patients had ≥1 non-elective hospitalisation within 1 year (Table 8.11). Of these patients, 41% and 14% had 2-3 and ≥4 non-elective hospitalisations respectively.

Table 8.11: Number of hospitalisations and length of stay in CHF patients within 1 year.

	CHF (N=467)
All admission (including same day discharge & elective admission)	189 (40%)
Non-elective admission (including same day discharge)	168 (36%)
Non-elective hospitalisation (excluding same day discharge)	150 (32%)
No of hosp.	
1	67 (14%)
2-3	62 (13%)
≥4	21 (5%)
Total LOS (days)	12 (5-24)
Avg LOS (days)	6 (3-11)

LOS= length of stay, Avg = average.

The non-elective hospitalisation rate was more than doubled in frail compared to non-frail patients (Table 8.12).

Table 8.12: Number of hospitalisations and length of stay within 1 year in frail vs non-frail patients by CFS, DI and 5MWT.

	CFS			DI			5MWT		
	F N=206	**NF** N=261	P	**F** N=165	**NF** N=302	P	**F** N=294	**NF** N=173	P
All admission (including same day discharge & elective admission)	112 (54%)	77 (30%)	*	100 (61%)	89 (29%)	*	145 (49%)	44 (25%)	*
Non-elective admission (including same day discharge)	104 (50%)	64 (25%)	*	94 (57%)	74 (25%)	*	135 (46%)	33 (19%)	*
Non-elective hospitalisation (excluding same day discharge)	96 (46%)	54 (21%)	*	87 (53%)	63 (20%)	*	122 (42%)	28 (16%)	*
No of hosp.			*			*			*
1	37 (18%)	30 (12%)		36 (22%)	31 (10%)		53 (18%)	14 (8%)	
2-3	46 (22%)	16 (6%)		37 (22%)	25 (8%)		52 (18%)	10 (6%)	
≥4	13 (6%)	8 (3%)		14 (9%)	7 (2%)		17 (6%)	4 (2%)	
Total LOS (days)	13 (5-26)	9 (3-22)	0.17	13 (6-29)	8 (3-22)	0.05	12 (5-26)	9 (3-18)	0.30
Avg LOS (days)	6 (4-11)	6 (2-12)	0.50	7 (4-12)	6 (2-11)	0.17	6 (4-12)	5 (3-10)	0.42

*P<0.001. CFS= clinical frailty scale, DI= deficit index, 5MWT= 5 meter walk test, LOS= length of stay, Avg = average, F = frail, NF= non-frail.

The relationship between number of hospitalisations and frailty categories are shown in Tables 8.13a-c. Worsening frailty was associated with increasing number of hospitalisations.

Table 8.13a: Number of hospitalisations within 1 year by categories of CFS.

		CFS					P
		Non-frail 1-3 (N=126)	Pre-frail 4 (N=135)	Mildly frail 5 (N=118)	Moderately frail 6 (N=69)	Severely frail ≥7 (N=19)	
No of hospitalisations	0	90% (N=113)	70% (N=94)	67% (N=79)	41% (N=28)	16% (N=3)	<0.001
	1	6% (N=8)	16% (N=22)	14% (N=17)	19% (N=13)	37% (N=7)	<0.001
	2-3	2% (N=3)	10% (N=13)	17% (N=20)	26% (N=18)	42% (N=8)	<0.001
	≥4	2% (N=2)	4% (N=6)	2% (N=2)	14% (N=10)	5% * (N=1)	<0.001

* The proportion of patients having ≥ 4 hospitalisations might not be accurate as these patients have a very high 1-year mortality rate of 74%.

Table 8.13b: Number of hospitalisations within 1 year by categories of DI.

		DI					P
		Non-frail 0.06-0.17 (N=88)	Pre-frail 0.18-0.23 (N=98)	Mildly frail 0.24-0.31 (N=93)	Moderately frail 0.32-0.41 (N=94)	Severely frail 0.42-0.72 (N=94)	
No of hospitalisations	0	90% (N=79)	86% (N=84)	70% (N=65)	57% (N=53)	38% (N=36)	<0.001
	1	7% (N=6)	9% (N=9)	14% (N=13)	17% (N=16)	24% (N=23)	<0.001
	2-3	1% (N=1)	4% (N=4)	14% (N=13)	20% (N=19)	27% (N=25)	<0.001
	≥4	2% (N=2)	1% (N=1)	2% (N=2)	6% (N=6)	11% (N=10)	<0.001

Table 8.13c: Number of hospitalisations within 1 year by categories of 5MWT.

		5MWT (sec)					P
		Non-frail ≤ 7 (N=195)	Pre-frail 7-9.5 (N=125)	Mildly frail 10-14.5 (N=67)	Moderately frail 15-28 (N=27)	Severely frail unable to complete (N=53)	
No of hospitalisations	0	83% (N=163)	68% (N=85)	61% (N=41)	33% (N=9)	36% (N=19)	<0.001
	1	9% (N=17)	15% (N=19)	14% (N=9)	33% (N=9)	25% (N=13)	<0.001
	2-3	6% (N=11)	12% (N=15)	22% (N=15)	26% (N=7)	26% (N=14)	<0.001
	≥4	2% (N=4)	5% (N=6)	3% (N=2)	8% (N=2)	13% (N=7)	<0.001

The cause of hospitalisations data is shown in Table 8.14. Most hospitalisations were due to non-cardiovascular causes (61%).

Table 8.14: Cause of hospitalisation of CHF patients within 1 year. (Expressed as number of hospitalisations, proportion of hospitalisations due to a specific cause)

Cause of Hosp	**CHF** (N=467) No of hosp = 322	Cause of Hosp	**CHF** (N=467) No of hosp = 322
Cardiovascular	124 (39%)	Non-cardiovascular	198 (61%)
HF	83 (26%)	Infection	67 (20%)
ACS	10 (3%)	Falls	52 (16%)
Angina	5 (2%)	AKI	22 (7%)
Arrhythmia	9 (3%)	Bleeding	6 (2%)
CVD	8 (2%)	Co-morbidities	42 (13%)
PVD	9 (3%)	COPD	20 (6%)
		Malignancy	6 (2%)
		Anaemia	4 (1%)
		General decline	3 (1%)
		Other	9 (3%)
		Medication-related	9 (3%)

Hosp= hospitalisation, ACS = acute coronary syndrome, CVD= cerebrovascular disease, PVD= peripheral vascular disease, AKI= acute kidney injury, COPD= chronic obstructive pulmonary disease.

Of non-cardiovascular hospitalisations, the commonest cause of hospitalisation was infection (34%), followed by falls (26%) and co-morbidities (21%). Of cardiovascular hospitalisations, the commonest cause of hospitalisation was decompensated HF (67%).

Comparing frail vs non-frail patients, the 2 commonest causes of hospitalisation in both groups were decompensated HF and infection (Table 8.15). Frail patients suffered more hospitalisations secondary to falls whereas non-frail patients suffered more hospitalisations secondary to co-morbidities.

Table 8.15: Cause of hospitalisation within 1 year in frail vs non-frail patients by CFS, DI and 5MWT.
(Expressed as number of hospitalisations, proportion of hospitalisations due to a specific cause)

Cause of Hospitalisation	CFS		DI		5MWT	
	F N=206 Hosp = 215	**NF** N=261 Hosp = 107	**F** N=165 Hosp = 215	**NF** N=302 Hosp = 107	**F** N=294 Hosp = 267	**NF** N=173 Hosp = 55
Non-cardiovascular	137 (64%)	61 (57%)	137 (64%)	61 (57%)	166 (62%)	32 (58%)
Infection	46 (22%)	21 (19%)	47 (23%)	20 (18%)	55 (21%)	12 (22%)
Falls	41 (19%)	11 (10%)	42 (20%)	10 (9%)	49 (18%)	3 (5%)
AKI	17 (8%)	5 (5%)	17 (8%)	5 (5%)	16 (6%)	6 (10%)
Bleeding	5 (2%)	1 (1%)	5 (2%)	1 (1%)	5 (2%)	1 (2%)
Co-morbidities	22 (10%)	20 (19%)	21 (9%)	21 (20%)	33 (12%)	9 (17%)
COPD	10 (5%)	10 (9%)	10 (5%)	10 (9%)	16 (6%)	4 (7%)
Malignancy	2 (1%)	4 (4%)	2 (1%)	4 (4%)	4 (1%)	2 (4%)
Anaemia	1 (0)	3 (3%)	1 (0)	3 (3%)	3 (1%)	1 (2%)
General decline	3 (1%)	0	3 (1%)	0	3 (1%)	0
Other	6 (3%)	3 (3%)	5 (2%)	4 (4%)	7 (3%)	2 (4%)
Medication-related	6 (3%)	3 (3%)	5 (2%)	4 (4%)	8 (3%)	1 (2%)

Table 8.15 (continued): Cause of hospitalisation within 1 year in frail vs non-frail patients by CFS, DI and 5MWT. (Expressed as number of hospitalisations, proportion of hospitalisations due to a specific cause)

Cause of Hospitalisation	CFS		DI		5MWT	
	F N=206 Hosp = 215	**NF** N=261 Hosp = 107	**F** N=165 Hosp = 215	**NF** N=302 Hosp = 107	**F** N=294 Hosp = 267	**NF** N=173 Hosp = 55
Cardiovascular	78 (36%)	46 (43%)	78 (36%)	46 (43%)	101 (38%)	23 (42%)
HF	46 (21%)	29 (26%)	56 (26%)	27 (24%)	70 (27%)	13 (24%)
ACS	6 (3%)	5 (5%)	6 (3%)	4 (4%)	6 (2%)	4 (7%)
Angina	8 (4%)	0	3 (1%)	2 (2%)	5 (2%)	0
Arrhythmia	5 (2%)	5 (5%)	5 (2%)	4 (4%)	6 (2%)	3 (5%)
CVD	6 (3%)	4 (4%)	4 (2%)	4 (4%)	6 (2%)	2 (4%)
PVD	7 (3%)	3 (3%)	4 (2%)	5 (5%)	8 (3%)	1 (2%)

ACS = acute coronary syndrome, CVD= cerebrovascular disease, PVD= peripheral vascular disease, AKI= acute kidney injury, COPD= chronic obstructive pulmonary disease, CFS= Clinical frailty scale, DI= Deficit index, 5MWT= 5 meter walk test, F=frail, NF= non-frail, Hosp= hospitalisation.

8.5 Discussion

This study is the first to make a comprehensive comparison of the prognostic value of several commonly used frailty tools in a well-characterised cohort of ambulatory patients with CHF. The main finding is that the presence of frailty was a powerful predictor of morbidity and mortality, regardless of the frailty tool used, and independent of age, co-morbidities, HF symptoms and severity. Moreover, the effect of frailty was 'dose-dependent' when measured quantitatively. Our results are consistent with results from other studies of HF cohorts which demonstrated frailty as a predictor of worse outcome (176, 177).

In this study, I have evaluated several commonly used frailty tools. Comprehensive assessment tools, such as Fried criteria, DI and EFS, cover multiple domains, including

physical function, nutrition, social support and co-morbidities, and provide strong prognostic information. However, their assessment requires a significant amount of time. Slow walking speed and weak handgrip strength evaluate only the physical phenotype of frailty but are both significant predictors of poor outcome (89, 90). Whilst the Fried criteria is the most commonly used frailty tool, it is complex to administer (178). This study showed that single physical tests are as effective at predicting mortality as lengthy assessment tools. The limitation with physical tests is that certain patients such as those with hemiplegia, advanced dementia or cognitive illness, might not be able to perform them.

Chapter 7 showed that screening tools such as AFN, DFI and CFS, are much easier to perform and can generally be completed within a minute. Amongst screening tools, we found that CFS has the highest prognostic value, comparable to that of complex assessment tools or physical tests. Therefore, in a busy clinical setting, physical tests or screening tools such as CFS, might be the preferred method for rapid evaluation of frailty. CFS might be a more appropriate initial evaluation tool, especially in patients admitted to hospital acutely unwell, who are unable to perform physical tests.

Frailty, ageing and HF are closely related and are not separate entities. A recent large-scale population study of 4 million individuals in the UK, showed that from 2002 to 2014, prevention of HF, either through better healthcare provision or more vigilant management of co-morbidities such as HTN, diabetes, AF and IHD, has delayed the onset of HF to a more advanced age (179). The consequence is an increased number of elderly patients with newly diagnosed HF. The profile of patients with HF is thus evolving over time with a trend towards older age and greater co-morbidity burden, indicating the need to re-evaluate our current model of care for HF.

Frailty used to be thought of as a ‘geriatric syndrome’ to be solely managed by geriatricians. There is an extensive literature on frailty and its impact in the general geriatric population, but there are few well-conducted studies evaluating frailty in patients with HF using validated frailty tools (156, 172). It is time for clinicians to rethink the management strategies for HF. The vast majority of HF patients seen in daily practice have profiles very different to those enrolled in contemporary clinical trials (180). They are mostly elderly, often socially isolated, have poor mobility and limited self-care ability; they are also more likely to be treated supportively, as they are less likely to tolerate

optimal doses of HF medications, all of which contribute to repeated hospitalisations and poor outcomes.

Traditional prognostic models for HF generally perform poorly in current populations because these models are mostly constructed using clinical variables; other important non-clinical factors such as frailty, social and functional status, are often not included (181). Similar to our findings, in a recent study conducted in patients requiring HF hospitalisations, measures of frailty have been shown to improve prediction of hospitalisation and death compared to conventional clinical risk predictors (182).

Whilst some might say that the symptoms of HF overlap with the components of frailty, this study showed that frailty is associated with worse outcome independent of NYHA class and other variables such as NT-proBNP and co-morbidities. Therefore, incorporating frailty into prognostic models of HF, might lead to a more holistic evaluation and improve identification of patients at greater risk.

Beyond simple prognostication, the clinical implications of identification of frailty in patients with HF are not clear. However, identification of 'pre-frailty' at an early stage might allow introduction of interventions such as cardiac rehabilitation, exercise training programmes, polypharmacy reduction, or nutritional optimisation, which might delay disability, improve QoL and symptoms and, perhaps, survival (183). Identification of frailty, especially those with moderate or severe frailty, might help decide on potential ceilings for future care.

8.6 Study limitations

Firstly, this study is a single-centre study with limited sample size, external validation of our results from other populations is needed. This study is, however, the most comprehensive study which compares the prognostic value of several commonly used frailty screening and assessment tools as well as physical tests in consecutive, unselected, patients with CHF.

Secondly, I have only studied 9 commonly used frailty tools. A large number of frailty tools have been proposed and identified patients at increased risk of adverse outcomes in other clinical scenarios (156).

Thirdly, this study has a limited follow up. Therefore, I am unable to comment on long-term prognostic significance of frailty in CHF patients. However, almost all patients identified as frail have had an end-point by the end of the study.

8.7 Conclusions

Frailty is a strong predictor of morbidity and mortality in ambulatory patients with CHF. Frailty evaluation should therefore be routinely performed in clinical practice to identify patients at high risk. CFS and 5MWT are simple screening tools that provide comparable prognostic information to assessment tools taking much longer to complete.

Chapter 9 Agreement and Classification Performance of Malnutrition Tools in Patients with Chronic Heart Failure

9.1 Chapter summary

Background: Malnutrition is common in patients with CHF. There are many malnutrition tools available but no standard method for evaluating malnutrition.

Objectives: To compare the prevalence of malnutrition, agreement and classification performance of 6 screening tools in patients with CHF.

Methods: I evaluated malnutrition using COntroling NUTritional Status (CONUT) score; Geriatric nutritional risk index (GNRI); Prognostic nutritional index (PNI); Malnutrition universal screening tool (MUST); Mini nutritional assessment-short form (MNA-SF); and Subjective global assessment (SGA). Since there is no "gold-standard" for malnutrition evaluation, for each of the malnutrition tools, I used the results of the other 5 tools to produce a standard combined index. Subjects were 'malnourished' if so identified by ≥ 3 out of 5 tools.

Results: I studied 467 consecutive CHF patients (67% male, median age 76 (IQR: 69-82) years, median NT-proBNP 1156 (IQR: 469-2463) ng/L). The prevalence of any degree and ≥ moderate malnutrition in CHF patients was 6-60% and 3-9% respectively.

Malnourished patients were older, had worse symptoms, higher NT-proBNP and more co-morbidities compared to non-malnourished patients. CONUT score had the highest sensitivity (80%), MNA-SF and SGA had the highest specificity (99%) and MNA-SF had the lowest misclassification rate (2%) in identifying ≥ moderate malnutrition as defined by the combined index.

Conclusion: Malnutrition is common in CHF patients. Its prevalence varies depending on the tool used. Amongst the malnutrition tools studied, MNA-SF has the best classification performance in identifying significant malnutrition as defined by the combined index.

9.2 Introduction

Although malnutrition is common in patients with CHF and is associated with increased morbidity and mortality, there is no standard method for evaluating malnutrition (118, 157). Several tools have been proposed. Multi-dimensional malnutrition tools, such as the subjective global assessment (SGA), predict mortality in patients with HF (184), but are time-consuming to perform. In contrast, simple screening tools, such as the geriatric nutritional risk index (GNRI), are also of prognostic value in patients with HF (118), but are easy and quick to perform. It is not clear whether simple malnutrition tools identify the same patients as multi-dimensional tools.

Previous studies have mostly evaluated malnutrition using individual tools in different populations and settings. Few studies have simultaneously evaluated different tools to quantify malnutrition in the same cohort of patients with CHF (97, 185). In this chapter, I will compare the prevalence of malnutrition, agreement and classification performance of several commonly used malnutrition tools (3 simple tools vs 3 multi-dimensional tools) in a cohort of ambulatory patients with CHF. I will also compare the prevalence of malnutrition in patients with CHF with those at risk of developing HF.

9.3 Methods

9.3.1 Study population

I prospectively recruited 467 consecutive ambulatory patients with CHF who attended our community HF clinic at Castle Hill Hospital, Hull, UK, between September 2016 and March 2017. I also prospectively recruited 87 individuals who had previously consented to take part in research at our department as controls. Control subjects were >65 years of age and had risk factors for developing HF. Details of the study population has been described in the 'methods' section of Chapter 7. All patients and controls had a full medical history, a physical examination and blood tests during baseline visit. A detailed description of relevant examinations can be found in Chapter 4.

9.3.2 Malnutrition evaluation

I evaluated malnutrition in CHF patients and controls using the following tools:

- Simple screening tools:
    1. COntroling NUTritional Status (CONUT) score
    2. Geriatric nutritional risk index (GNRI)
    3. Prognostic nutritional index (PNI)
- Multi-dimensional tools:
    1. Malnutrition universal screening tool (MUST)
    2. Mini nutritional assessment-short form (MNA-SF)
    3. Subjective global assessment (SGA)
- Laboratory tests:
    1. Serum total cholesterol
    2. Serum albumin level
    3. Serum total lymphocyte count

The entire malnutrition evaluation process took an hour per patient. A description of the malnutrition evaluation process can be found in the 'malnutrition evaluation' section of Chapter 4.

9.3.3 Statistical analysis

Routine statistical analyses have been detailed in Chapter 4. Firstly, I compared the prevalence of malnutrition using different tools. Then, I used Venn diagrams to illustrate the relationship amongst malnutrition tools. Next, I used Kappa statistics to study the agreement amongst malnutrition tools.

Since there is no gold standard in evaluating malnutrition in patients with CHF, for each of the screening tools, I used the results of the *other* 5 tools to produce a single combined malnutrition index, which I assumed to be the gold standard malnutrition tool. This methodology has previously been suggested by Pablo and colleagues (171). I defined subjects as malnourished if so identified by at least 3 of the 5 tools. In a separate analysis, in order to assess the value of laboratory tests (cholesterol, albumin and total lymphocyte

count) in defining malnutrition, I compared each with a similar combined index derived from the malnutrition tools that did not contain the variable in question. I then calculated the sensitivity, specificity and predictive values for each of the malnutrition tools and laboratory tests in identifying malnutrition according to the combined index.

To investigate the bias associated with SGA being a subjective malnutrition tool, in addition to myself, I also invited a second investigator, a research nurse (JW), to complete the SGA for a random sample of 23 patients. I then used Kappa statistics to determine the inter-operator agreement.

During data analysis, it quickly became apparent that the CONUT score was reporting a disproportionately large number of subjects as having malnutrition of some degree. I therefore performed additional analyses to study subjects with *at least (≥) moderate* malnutrition.

9.4 Results

9.4.1 Baseline characteristics

The baseline characteristics of CHF patients and controls have been shown in Table 7.1.

9.4.2 Prevalence of Malnutrition

Malnutrition of any degree

The prevalence of malnutrition of any degree in patients with CHF was highly variable, ranging from 6-60%, depending on the malnutrition tool used (Figure 9.1a-b). CONUT score classified a much larger proportion of subjects (both CHF patients and controls) as malnourished by any degree than other tools. Malnutrition was much more common in patients with CHF than in controls. For this reason, I focused the rest of this chapter on studying malnutrition in CHF patients.

Figure 9.1a: Prevalence of malnutrition by simple screening tools.

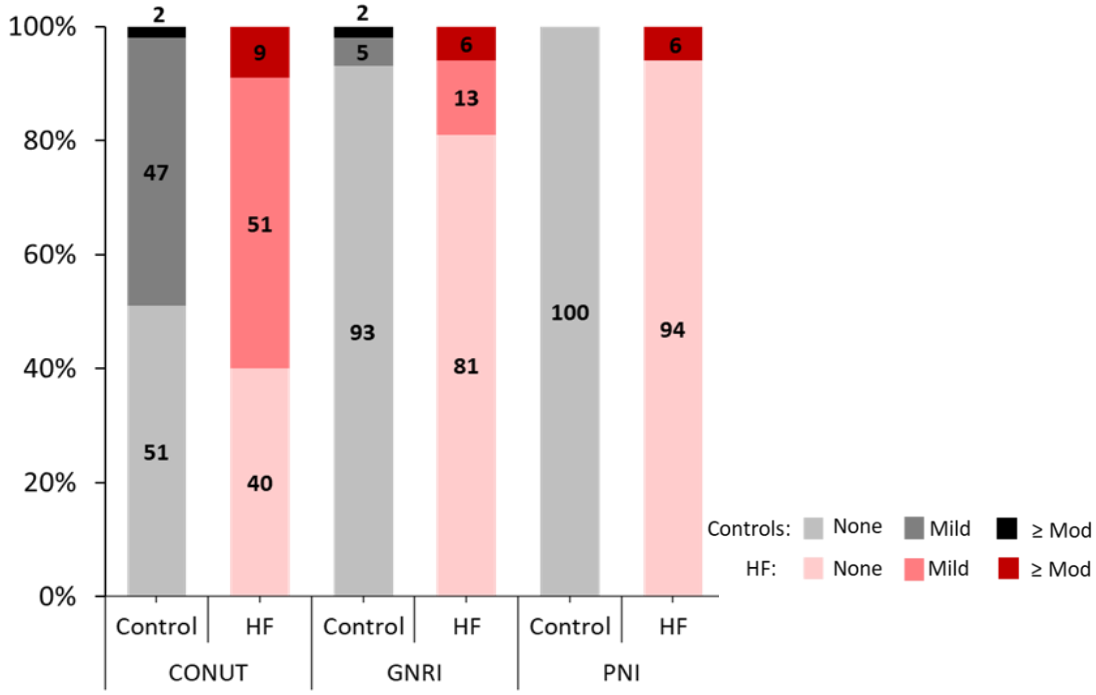
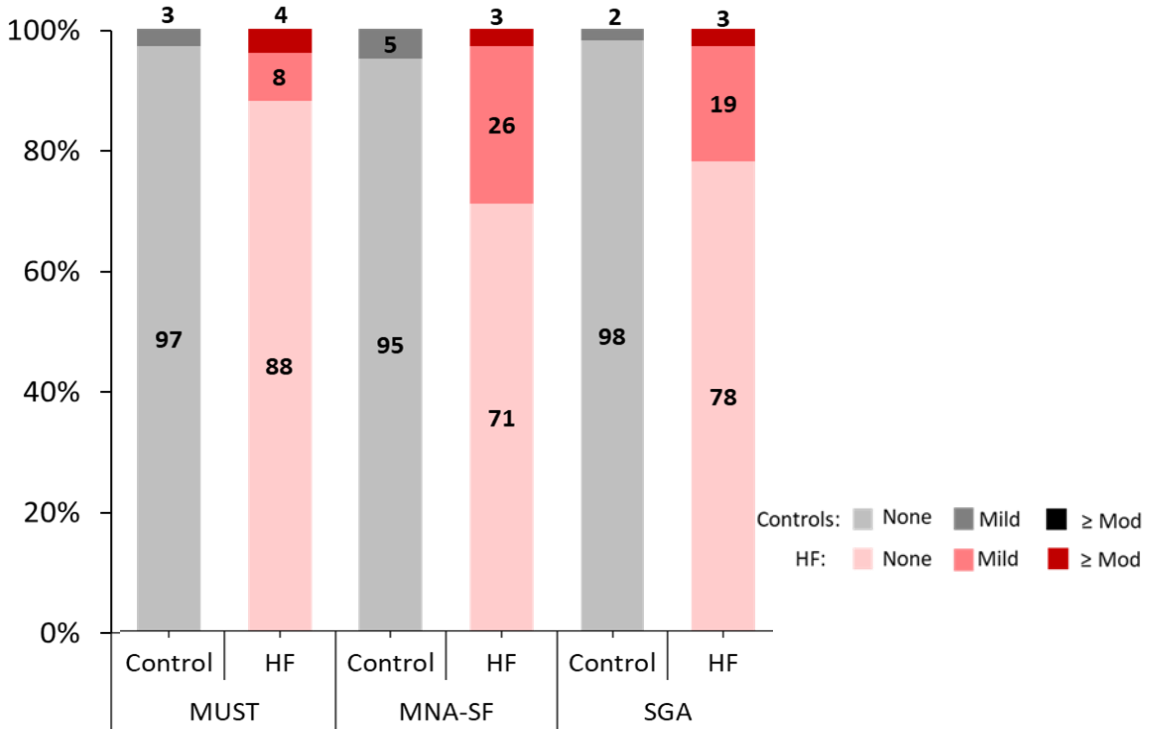


Figure 9.1b: Prevalence of malnutrition by multi-dimensional screening tools.

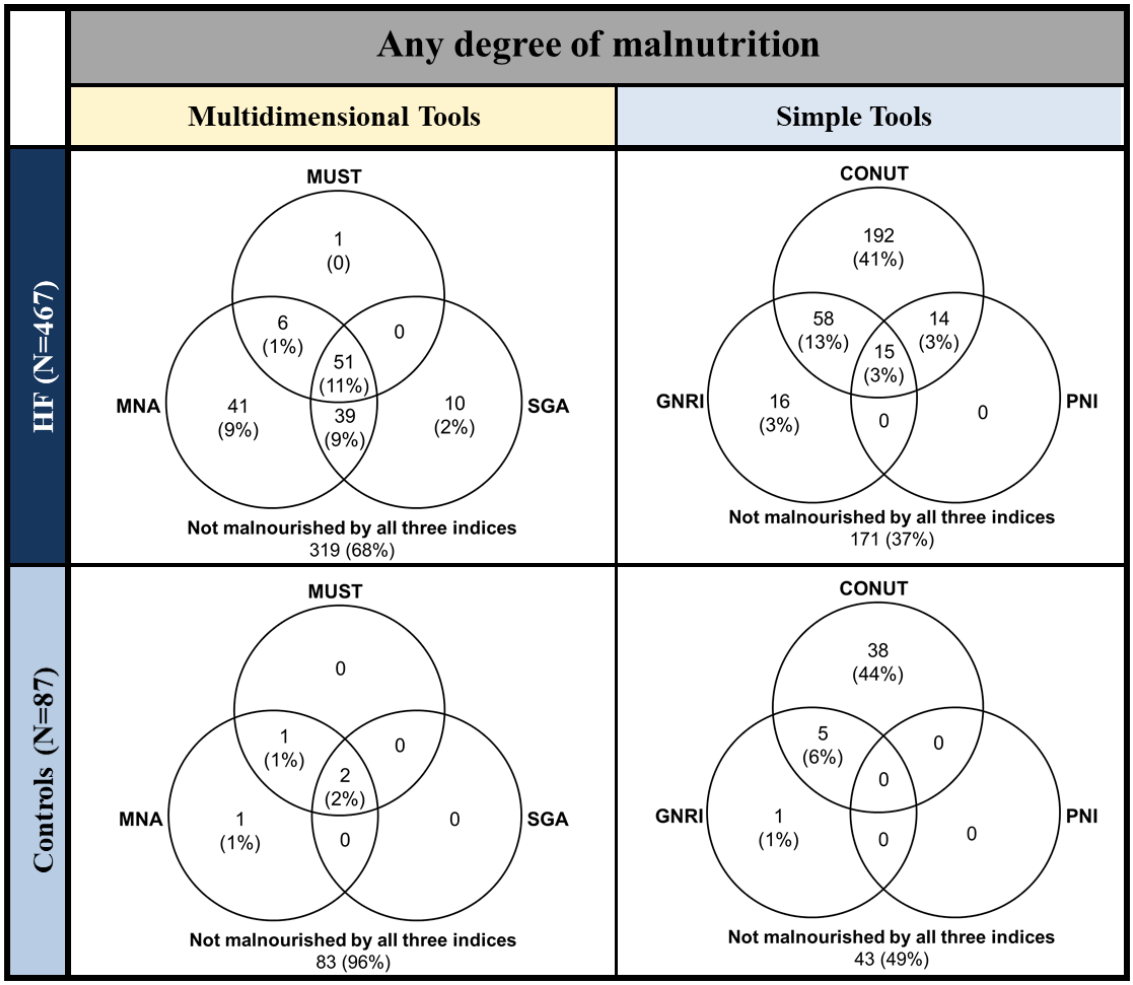


CONUT = Controlling nutritional status, GNRI = Geriatric nutritional risk index, PNI = Prognostic nutritional index, MUST= malnutrition universal screening tool, MNA-SF = mini nutritional assessment – short form, SGA= subjective global assessment

Amongst the simple screening tools, CONUT score graded the greatest proportion while PNI graded the lowest proportion of patients as malnourished by any degree (Figures 9.1a & 9.2a). Only 3% (N=15) of patients were classified as malnourished by any degree by all 3 simple screening tools (Figure 9.2a, top right).

Amongst the multi-dimensional screening tools, MNA-SF graded the greatest proportion whilst the MUST score graded the lowest proportion of patients as malnourished by any degree (Figures 9.1b & 9.2a). Only 11% (N=51) of patients were classified as malnourished by any degree by all 3 multi-dimensional screening tools (Figure 9.2a, top left).

Figure 9.2a: Relationship amongst malnutrition tools in detecting malnutrition (any degree) in CHF patients vs controls.



CONUT = Controlling nutritional status, GNRI = Geriatric nutritional risk index, PNI = Prognostic nutritional Index, MUST= malnutrition universal screening tool, MNA-SF = mini nutritional assessment – short form, SGA= subjective global assessment.

The prevalence of malnutrition of any degree was similar in patients with HeFNEF versus HeFREF but was generally more common in patients with AF versus SR (Table 9.1). The prevalence of malnutrition of any degree increased with decreasing BMI and increasing NYHA class, age and NT-proBNP (Table 9.1).

Table 9.1: Prevalence of malnutrition (any degree) in different subgroups of CHF patients.

		Multi-dimensional tools			Simple tools		
		MUST	**MNA**	**SGA**	**GNRI**	**CONUT**	**PNI**
		(N=58)	(N=137)	(N=100)	(N=89)	(N=279)	(N=29)
Rhythm	**SR**	10%	25%	18%	21%	54%	4%
	(N=252)	(N=25)	(N=62)	(N=45)	(N=52)	(N=137)	(N=11)
	AF	15%	35%	26%	17%	66%	8%
	(N=215)	(N=33)	(N=75)	(N=55)	(N=37)	(N=142)	(N=18)
	P	0.08	0.02	0.04	0.35	0.009	0.07
BMI (kg/m^2)	**<24.9**	34%	56%	62%	69%	72%	10%
	(N=111)	(N=38)	(N=62)	(N=69)	(N=77)	(N=80)	(N=11)
	25.0-29.9	9%	23%	16%	8%	58%	7%
	(N=158)	(N=14)	(N=37)	(N=25)	(N=12)	(N=91)	(N=11)
	≥30	3%	19%	3%	0	55%	4%
	(N=198)	(N=6)	(N=38)	(N=6)		(N=108)	(N=7)
	P	<0.001	<0.001	<0.001	<0.001	0.01	0.07
HF phenotype	**HeFREF**	11%	30%	21%	20%	60%	6%
	(N=291)	(N=32)	(N=86)	(N=61)	(N=57)	(N=174)	(N=17)
	HeFNEF	15%	29%	22%	18%	60%	7%
	(N=176)	(N=26)	(N=51)	(N=39)	(N=32)	(N=105)	(N=12)
	P	0.23	0.90	0.76	0.71	0.97	0.67
NYHA	**I/II**	10%	23%	18%	18%	58%	4%
	(N=364)	(N=35)	(N=84)	(N=65)	(N=66)	(N=210)	(N=16)
	III/IV	22%	52%	34%	22%	67%	13%
	(N=103)	(N=23)	(N=53)	(N=35)	(N=23)	(N=69)	(N=13)
	P	0.001	<0.001	<0.001	0.34	0.10	0.002

Table 9.1 (continued): Prevalence of malnutrition (any degree) in different subgroups of CHF patients.

		Multi-dimensional tools			Simple tools		
		MUST (N=58)	**MNA** (N=137)	**SGA** (N=100)	**GNRI** (N=89)	**CONUT** (N=279)	**PNI** (N=29)
NT-proBNP (ng/L)	**<1000** (N=215)	6% (N=13)	18% (N=39)	12% (N=26)	14% (N=29)	48% (N=104)	3% (N=7)
	1000-2000 (N=108)	11% (N=12)	29% (N=31)	17% (N=18)	17% (N=18)	61% (N=66)	5% (N=5)
	>2000 (N=144)	23% (N=33)	47% (N=67)	39% (N=56)	29% (N=42)	76% (N=109)	12% (N=17)
	P	<0.001	<0.001	<0.001	0.001	<0.001	0.003
Age (years)	**<65** (N=82)	6% (N=5)	20% (N=16)	7% (N=6)	6% (N=5)	37% (N=30)	2% (N=2)
	65-75 (N=139)	6% (N=8)	19% (N=26)	9% (N=12)	9% (N=12)	58% (N=80)	8% (N=6)
	>75 (N=246)	18% (N=45)	39% (N=95)	33% (N=82)	29% (N=72)	69% (N=169)	8% (N=19)
	P	<0.001	<0.001	<0.001	<0.001	<0.001	0.22

MUST= malnutrition universal screening tool, MNA= mini nutritional assessment – short form, SGA= subjective global assessment, GNRI= geriatric nutritional risk index, CONUT= controlling nutritional status index, PNI= prognostic nutritional index, SR= sinus rhythm, AF= atrial fibrillation, BMI= body mass index, HeFREF= heart failure with reduced ejection fraction, HeFNEF= heart failure with normal ejection fraction, NYHA= New York Heart Association, NT-proBNP= N-terminal pro B type natriuretic peptide.

At least moderate malnutrition

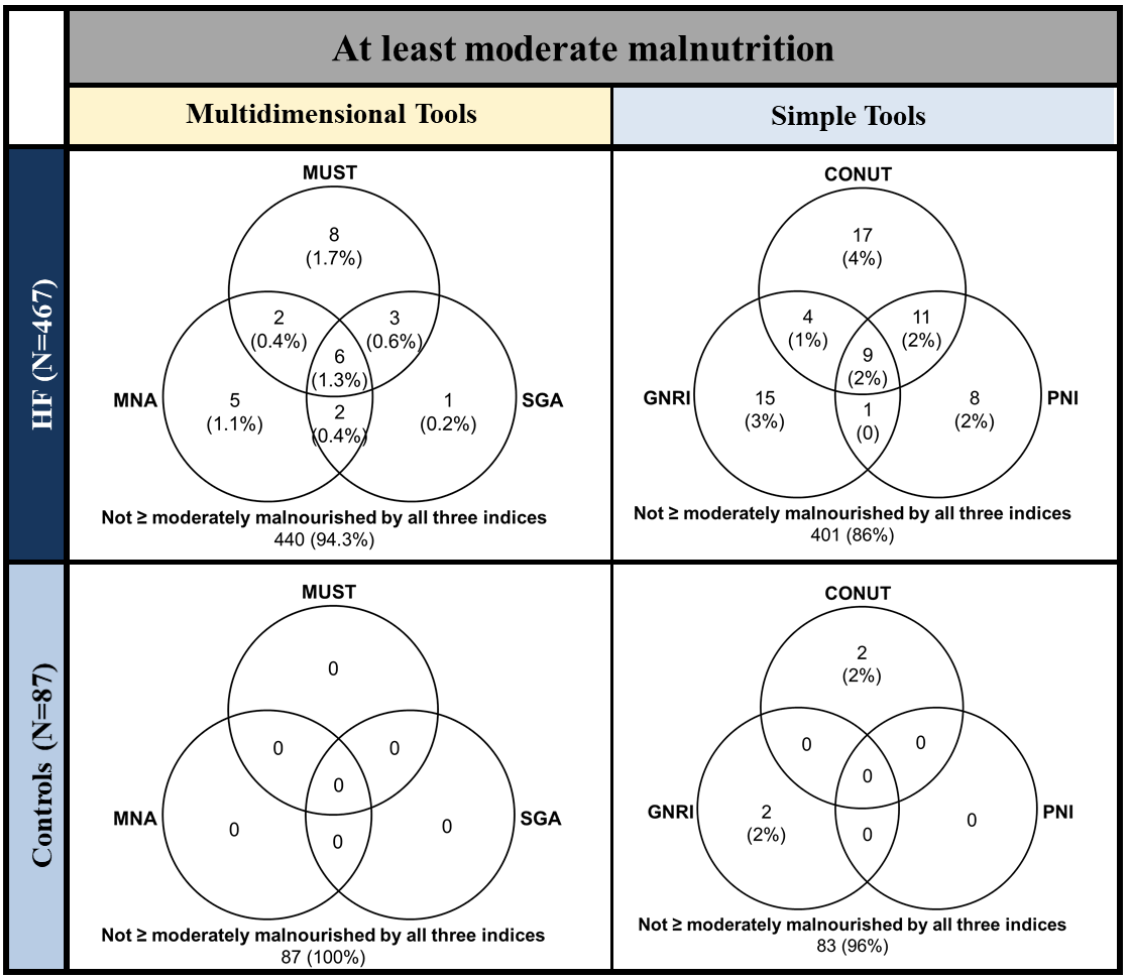
The prevalence of ≥moderate malnutrition in patients with CHF ranged from 3-9%, depending on the malnutrition tool used (Figure 9.1a-b). It was much more common in patients with CHF than in controls.

Amongst the simple screening tools, CONUT score graded the greatest proportion of patients as having ≥moderate malnutrition (Figures 9.1a & 9.2b). Only 2% (N=9) of

patients were classified as having ≥moderate malnutrition by all 3 simple screening tools (Figure 9.2b, top right).

Amongst the multi-dimensional screening tools, MUST score graded the greatest proportion of patients as having ≥moderate malnutrition (Figures 9.1b & 9.2b). Only 1.3% (N=6) of patients were classified as having ≥moderate malnutrition by all 3 multi-dimensional screening tools (Figure 9.2b, top left).

Figure 9.2b: Relationship amongst malnutrition tools in detecting malnutrition (≥moderate) in CHF patients vs controls.



CONUT = Controlling nutritional status, GNRI = Geriatric nutritional risk index, PNI = Prognostic nutritional Index, MUST= malnutrition universal screening tool, MNA-SF = mini nutritional assessment – short form, SGA= subjective global assessment.

The prevalence of ≥moderate malnutrition was similar in patients with HeFNEF versus HeFREF and in patients with AF versus SR (Table 9.2). The prevalence of ≥moderate

malnutrition increased with decreasing BMI and increasing NYHA class and NT-proBNP (Table 9.2).

Table 9.2: Prevalence of malnutrition (≥moderate) in different subgroups of CHF patients.

		Multi-dimensional tools			Simple tools		
		MUST (N=19)	**MNA** (N=15)	**SGA** (N=12)	**GNRI** (N=29)	**CONUT** (N=41)	**PNI** (N=29)
Rhythm	**SR** (N=252)	4% (N=10)	2% (N=5)	2% (N=4)	7% (N=17)	6% (N=16)	4% (N=11)
	AF (N=215)	4% (N=9)	5% (N=10)	4% (N=8)	6% (N=12)	12% (N=25)	8% (N=18)
	P	0.91	0.10	0.15	0.60	0.04	0.07
BMI (kg/m^2)	**<24.9** (N=111)	13% (N=14)	10% (N=11)	9% (N=10)	26% (N=29)	18% (N=20)	10% (N=11)
	25.0-29.9 (N=158)	2% (N=3)	1% (N=2)	1% (N=2)	0	8% (N=12)	7% (N=11)
	≥30 (N=198)	1% (N=2)	1% (N=2)	0	0	5% (N=9)	4% (N=7)
	P	<0.001	<0.001	<0.001	<0.001	<0.001	0.07
HF phenotype	**HeFREF** (N=291)	5% (N=13)	3% (N=9)	2% (N=6)	6% (N=18)	9% (N=26)	6% (N=17)
	HeFNEF (N=176)	3% (N=6)	3% (N=6)	3% (N=6)	6% (N=11)	9% (N=15)	7% (N=12)
	P	0.58	0.85	0.37	0.98	0.89	0.67
NYHA	**I/II** (N=364)	3% (N=12)	2% (N=7)	1% (N=5)	6% (N=21)	6% (N=22)	4% (N=16)
	III/IV (N=103)	7% (N=7)	8% (N=8)	7% (N=7)	8% (N=8)	18% (N=19)	13% (N=13)
	P	0.11	0.003	0.002	0.46	<0.001	0.002

Table 9.2 (continued): Prevalence of malnutrition (≥moderate) in different subgroups of CHF patients.

		Multi-dimensional tools			Simple tools		
		MUST (N=19)	**MNA** (N=15)	**SGA** (N=12)	**GNRI** (N=29)	**CONUT** (N=41)	**PNI** (N=29)
NT-proBNP (ng/L)	**<1000** (N=215)	1% (N=2)	1% (N=1)	0	3% (N=7)	5% (N=10)	3% (N=7)
	1000-2000 (N=108)	4% (N=4)	1% (N=1)	1% (N=1)	7% (N=8)	6% (N=6)	5% (N=5)
	>2000 (N=144)	9% (N=13)	9% (N=13)	8% (N=11)	10% (N=14)	18% (N=25)	12% (N=17)
	P	0.001	<0.001	<0.001	0.04	<0.001	0.003
Age (years)	**<65** (N=82)	1% (N=1)	0	0	2% (N=2)	2% (N=2)	2% (N=2)
	65-75 (N=139)	2% (N=3)	2% (N=3)	2% (N=3)	3% (N=4)	6% (N=8)	6% (N=8)
	>75 (N=246)	6% (N=15)	5% (N=12)	4% (N=9)	9% (N=23)	13% (N=31)	8% (N=19)
	P	0.06	0.07	0.18	0.01	0.006	0.22

MUST= malnutrition universal screening tool, MNA= mini nutritional assessment – short form, SGA= subjective global assessment, GNRI= geriatric nutritional risk index, CONUT= controlling nutritional status index, PNI= prognostic nutritional index, SR= sinus rhythm, AF= atrial fibrillation, BMI= body mass index, HeFREF= heart failure with reduced ejection fraction, HeFNEF= heart failure with normal ejection fraction, NYHA= New York Heart Association, NT-proBNP= N-terminal pro B type natriuretic peptide.

9.4.3 Relation between malnutrition and clinical data

Malnutrition of any degree

Compared to those with normal nutritional status, patients with malnutrition of any degree were older, had a lower BMI; more co-morbidities, worse symptoms, higher NT-proBNP and lower Hb. They were also less likely to be on an ACEi/ARB or a statin. (Tables 9.3a-c)

Table 9.3a: Baseline characteristics of malnourished (any degree) vs non-malnourished CHF patients by MUST.

	Non-mal N=409	**Mal** N=58	**P**
Demographics			
Age (years)	75 (69-82)	81 (76-85)	<0.001
Sex (male), n (%)	277 (68)	36 (62)	0.39
BP systolic (mmHg)	139 (126-162)	137 (122-153)	0.73
BP diastolic (mmHg)	75 (67-83)	71 (60-82)	0.05
HR (bpm)	70 (60-80)	74 (62-83)	0.26
Height (m)	1.69 (1.61-1.75)	1.66 (1.60-1.71)	0.05
Weight (kg)	85 (72-100)	62 (52-78)	<0.001
BMI (kg/m^2)	29.5 (26.4-33.9)	22.3 (19.6-26.7)	<0.001
NYHA III/IV, n (%)	80 (20)	23 (40)	0.001
HeFREF, n (%)	259 (63)	32 (55)	0.23
HeFNEF, n (%)	150 (37)	26 (45)	
Co-morbidities			
MI, n (%)	173 (42)	25 (43)	0.91
PVD, n (%)	59 (14)	13 (22)	0.12
HTN, n (%)	274 (67)	39 (67)	0.97
CVD, n (%)	59 (14)	12 (21)	0.21
Diabetes Mellitus, n (%)	142 (34)	21 (36)	0.88
Dementia, n (%)	32 (8)	16 (28)	<0.001
COPD, n (%)	113 (28)	27 (47)	0.003
Depression, n (%)	72 (18)	21 (36)	0.001
Anaemia, n (%)	179 (44)	39 (67)	0.001
Falls, n (%)	138 (34)	35 (60)	<0.001
Urinary incontinence, n (%)	173 (42)	25 (43)	0.91
Charlson Score	8 (6-10)	10 (8-11)	<0.001

Table 9.3a (continued): Baseline characteristics of malnourished (any degree) vs non-malnourished CHF patients by MUST.

	Non-mal N=409	**Mal** N=58	**P**
Medications			
ACEi/ARB, n (%)	351 (86)	38 (66)	<0.001
BB, n (%)	347 (85)	45 (78)	0.16
MRA, n (%)	193 (47)	21 (36)	0.12
Loop diuretics, n (%)	304 (74)	43 (74)	0.98
Thiazide diuretics, n (%)	15 (4)	2 (3)	0.93
Digoxin, n (%)	82 (20)	18 (31)	0.06
Statin, n (%)	258 (63)	32 (55)	0.25
≥5 medications, n (%)	351 (86)	53 (91)	0.25
Blood tests			
NT-proBNP (ng/L)	1020 (436-2124)	2465 (1372-4143)	<0.001
Hb (g/dL)	13.2 (12.0-14.3)	12.1 (11.0-13.1)	<0.001
Sodium (mmol/L)	137 (135-138)	136 (133-138)	0.05
Potassium (mmol/L)	4.4 (4.2-4.7)	4.3 (4.1-4.8)	0.32
eGFR (ml/min/1.73 m^2)	59 (37-76)	55 (40-73)	0.99

Table 9.3b: Baseline characteristics of malnourished (any degree) vs non-malnourished CHF patients by MNA-SF.

	Non-mal N=330	**Mal** N=137	**P**
Demographics			
Age (years)	75 (68-81)	80 (74-86)	<0.001
Sex (male), n (%)	227 (69)	86 (63)	0.21
BP systolic (mmHg)	142 (126-164)	135 (122-154)	0.03
BP diastolic (mmHg)	76 (68-83)	71 (63-81)	<0.001
HR (bpm)	70 (60-80)	70 (60-83)	0.35
Height (m)	1.69 (1.62-1.75)	1.65 (1.59-1.75)	0.07
Weight (kg)	86 (74-101)	73 (59-90)	<0.001
BMI (kg/m^2)	29.7 (26.8-34.3)	25.8 (21.7-30.6)	<0.001
NYHA III/IV, n (%)	50 (15)	53 (39)	<0.001
HeFREF, n (%)	205 (62)	86 (63)	0.90
HeFNEF, n (%)	125 (38)	51 (37)	
Co-morbidities			
MI, n (%)	134 (41)	64 (47)	0.22
PVD, n (%)	44 (13)	28 (20)	0.05
HTN, n (%)	224 (68)	89 (65)	0.54
CVD, n (%)	42 (13)	29 (21)	0.02
Diabetes Mellitus, n (%)	109 (33)	54 (40)	0.13
Dementia, n (%)	12 (4)	36 (26)	<0.001
COPD, n (%)	90 (27)	50 (37)	0.05
Depression, n (%)	43 (13)	50 (37)	<0.001
Anaemia, n (%)	123 (37)	95 (69)	<0.001
Falls, n (%)	94 (29)	79 (58)	<0.001
Urinary incontinence, n (%)	16 (5)	17 (12)	0.004
Charlson Score	8 (6-9)	10 (8-11)	<0.001

Table 9.3b (continued): Baseline characteristics of malnourished (any degree) vs non-malnourished CHF patients by MNA-SF.

	Non-mal N=330	**Mal** N=137	**P**
Medications			
ACEi/ARB, n (%)	292 (89)	97 (71)	<0.001
BB, n (%)	281 (85)	111 (81)	0.27
MRA, n (%)	157 (48)	57 (42)	0.24
Loop diuretics, n (%)	234 (71)	113 (83)	0.009
Thiazide diuretics, n (%)	8 (2)	9 (7)	0.03
Digoxin, n (%)	64 (19)	36 (26)	0.10
Statin, n (%)	219 (66)	71 (52)	0.003
≥5 medications, n (%)	278 (84)	126 (92)	0.03
Blood tests			
NT-proBNP (ng/L)	903 (401-1798)	1963 (926-3655)	<0.001
Hb (g/dL)	13.4 (12.2-14.4)	12.1 (11.1-13.2)	<0.001
Sodium (mmol/L)	137 (135-139)	136 (134-138)	0.04
Potassium (mmol/L)	4.5 (4.2-4.7)	4.3 (4.1-4.7)	0.01
eGFR (ml/min/1.73 m^2)	57 (43-75)	50 (34-69)	0.004

Table 9.3c: Baseline characteristics of malnourished (any degree) vs non-malnourished CHF patients by SGA.

	Non-mal N=367	**Mal** N=100	**P**
Demographics			
Age (years)	74 (67-80)	84 (78-88)	<0.001
Sex (male), n (%)	253 (69)	60 (60)	0.09
BP systolic (mmHg)	139 (125-164)	137 (127-157)	0.33
BP diastolic (mmHg)	75 (67-84)	71 (62-80)	0.002
HR (bpm)	70 (61-80)	70 (60-83)	0.97
Height (m)	1.69 (1.62-1.75)	1.65 (1.58-1.72)	<0.001
Weight (kg)	89 (75-102)	61 (52-74)	<0.001
BMI (kg/m^2)	30.2 (27.2-34.7)	22.8 (20.8-25.8)	<0.001
NYHA III/IV, n (%)	68 (18)	35 (35)	<0.001
HeFREF, n (%)	230 (63)	61 (61)	0.76
HeFNEF, n (%)	137 (37)	39 (39)	
Co-morbidities			
MI, n (%)	154 (42)	44 (44)	0.72
PVD, n (%)	52 (14)	20 (20)	0.15
HTN, n (%)	248 (68)	65 (65)	0.63
CVD, n (%)	52 (14)	19 (19)	0.23
Diabetes Mellitus, n (%)	135 (37)	28 (28)	0.23
Dementia, n (%)	19 (5)	29 (29)	<0.001
COPD, n (%)	101 (28)	39 (39)	0.03
Depression, n (%)	56 (15)	37 (37)	<0.001
Anaemia, n (%)	145 (40)	73 (73)	<0.001
Falls, n (%)	109 (30)	64 (64)	<0.001
Urinary incontinence, n (%)	20 (5)	13 (13)	0.009
Charlson Score	8 (6-9)	10 (8-11)	<0.001

Table 9.3c (continued): Baseline characteristics of malnourished (any degree) vs non-malnourished CHF patients by SGA.

	Non-mal N=367	Mal N=100	P
Medications			
ACEi/ARB, n (%)	321 (88)	68 (68)	<0.001
BB, n (%)	313 (85)	79 (79)	0.13
MRA, n (%)	174 (47)	40 (40)	0.19
Loop diuretics, n (%)	269 (73)	78 (78)	0.34
Thiazide diuretics, n (%)	11 (3)	6 (6)	0.16
Digoxin, n (%)	73 (20)	27 (27)	0.12
Statin, n (%)	243 (66)	47 (47)	<0.001
≥5 medications, n (%)	313 (85)	91 (91)	0.14
Blood tests			
NT-proBNP (ng/L)	963 (426-1919)	2613 (1013-4712)	<0.001
Hb (g/dL)	13.4 (12.1-14.4)	12.0 (10.9-13.1)	<0.001
Sodium (mmol/L)	137 (135-138)	136 (134-138)	0.22
Potassium (mmol/L)	4.5 (4.2-4.7)	4.3 (4.1-4.6)	0.007
eGFR (ml/min/1.73 m^2)	56 (41-74)	52 (33-70)	0.02

HR= heart rate, BP= blood pressure, NYHA= New York Heart Association, HeFREF= heart failure with reduced ejection fraction, HeFNEF= heart failure with normal ejection fraction, BMI= body mass index, MI= myocardial infarction, PVD= peripheral vascular disease, HTN= hypertension, CVD= cerebrovascular disease, COPD= chronic obstructive pulmonary disease, BB= beta-blocker, ACEi= angiotensin converting enzyme inhibitor, ARB= angiotensin receptor blocker, MRA= mineralocorticoid receptor antagonist, NT-proBNP= N-terminal pro-B-type natriuretic peptide, Hb= haemoglobin, eGFR = estimated glomerular filtration rate, MUST = malnutrition universal screening tool, MNA-SF = mini nutritional assessment short form, SGA = subjective global assessment, mal= malnourished.

At least moderate malnutrition

Compared to those with normal nutritional status or mild malnutrition, patients with ≥moderate malnutrition were older, had a lower BMI, more co-morbidities, worse symptoms, higher NT-proBNP and lower Hb (Table 9.4a-c). They were also less likely to be on ACEi/ ARB or a statin.

Table 9.4a: Baseline characteristics of CHF patients with ≥moderate vs <moderate malnutrition by MUST.

Malnutrition	**< Mod** N=448	**≥ Mod** N=19	**P**
Demographics			
Age (years)	76 (69-82)	79 (76-85)	0.04
Sex (male), n (%)	299 (67)	14 (74)	0.53
BP systolic (mmHg)	139 (126-162)	135 (122-149)	0.49
BP diastolic (mmHg)	75 (67-83)	72 (61-78)	0.08
HR (bpm)	70 (60-80)	70 (59-81)	0.93
Height (m)	1.69 (1.61-1.75)	1.65 (1.62-1.67)	0.05
Weight (kg)	83 (70-99)	52 (47-67)	<0.001
BMI (kg/m^2)	29.2 (25.6-33.3)	19.7 (17.9-25.2)	<0.001
NYHA III/IV, n (%)	96 (21)	7 (37)	0.11
HeFREF, n (%)	278 (62)	13 (68)	0.58
HeFNEF, n (%)	170 (38)	6 (32)	
Co-morbidities			
MI, n (%)	190 (42)	8 (42)	0.98
PVD, n (%)	67 (15)	5 (26)	0.18
HTN, n (%)	300 (67)	13 (68)	0.90
CVD, n (%)	66 (15)	5 (26)	0.17
Diabetes Mellitus, n (%)	158 (35)	5 (26)	0.42
Dementia, n (%)	42 (9)	6 (32)	0.002
COPD, n (%)	131 (29)	9 (47)	0.09
Depression, n (%)	86 (19)	7 (37)	0.06
Anaemia, n (%)	201 (45)	17 (90)	<0.001
Falls, n (%)	164 (37)	9 (47)	0.34
Urinary incontinence, n (%)	32 (7)	1 (5)	0.75
Charlson Score	8 (6-10)	10 (8-10)	0.03

Table 9.4a (continued): Baseline characteristics of CHF patients with ≥moderate vs <moderate malnutrition by MUST.

Malnutrition	**< Mod** N=448	**≥ Mod** N=19	**P**
Medications			
ACEi/ARB, n (%)	375 (84)	14 (74)	0.25
BB, n (%)	376 (84)	16 (84)	0.97
MRA, n (%)	207 (46)	7 (37)	0.42
Loop diuretics, n (%)	334 (75)	13 (68)	0.55
Thiazide diuretics, n (%)	15 (3)	2 (11)	0.10
Digoxin, n (%)	94 (21)	6 (32)	0.27
Statin, n (%)	281 (63)	9 (47)	0.18
≥5 medications, n (%)	386 (86)	18 (95)	0.28
Blood tests			
NT-proBNP (ng/L)	1092 (482-2304)	3783 (1624-7177)	<0.001
Hb (g/dL)	13.1 (11.9-14.3)	12.0 (10.8-12.6)	0.001
Sodium (mmol/L)	137 (135-138)	135 (132-138)	0.07
Potassium (mmol/L)	4.4 (4.2-4.7)	4.4 (3.8-4.7)	0.17
eGFR (ml/min/1.73 m^2)	55 (40-73)	61 (43-82)	0.44

Table 9.4b: Baseline characteristics of CHF patients with ≥moderate vs <moderate malnutrition by MNA-SF.

Malnutrition	**< Mod** N=452	**≥ Mod** N=15	**P**
Demographics			
Age (years)	76 (69-82)	82 (76-91)	0.004
Sex (male), n (%)	303 (67)	10 (67)	0.98
BP systolic (mmHg)	140 (126-162)	128 (104-136)	0.002
BP diastolic (mmHg)	75 (67-83)	60 (58-71)	0.001
HR (bpm)	70 (60-80)	80 (64-85)	0.17
Height (m)	1.69 (1.61-1.75)	1.65 (1.60-1.72)	0.29
Weight (kg)	83 (70-99)	57 (50-72)	<0.001
BMI (kg/m^2)	29.2 (25.6-33.3)	20.8 (19.1-25.2)	<0.001
NYHA III/IV, n (%)	95 (21)	8 (53)	0.003
HeFREF, n (%)	282 (62)	9 (60)	0.85
HeFNEF, n (%)	170 (38)	6 (40)	
Co-morbidities			
MI, n (%)	195 (43)	3 (20)	0.07
PVD, n (%)	66 (15)	6 (40)	0.007
HTN, n (%)	306 (68)	7 (47)	0.09
CVD, n (%)	69 (15)	2 (13)	0.84
Diabetes Mellitus, n (%)	158 (35)	5 (33)	0.90
Dementia, n (%)	40 (9)	8 (53)	<0.001
COPD, n (%)	133 (29)	7 (47)	0.15
Depression, n (%)	87 (19)	6 (40)	0.05
Anaemia, n (%)	207 (46)	11 (73)	0.04
Falls, n (%)	162 (36)	11 (73)	0.003
Urinary incontinence, n (%)	28 (6)	5 (33)	<0.001
Charlson Score	8 (6-10)	10 (9-11)	0.01

Table 9.4b (continued): Baseline characteristics of CHF patients with ≥moderate vs <moderate malnutrition by MNA-SF.

Malnutrition	**< Mod** N=452	**≥ Mod** N=15	**P**
Medications			
ACEi/ARB, n (%)	382 (85)	7 (47)	<0.001
BB, n (%)	378 (84)	14 (93)	0.31
MRA, n (%)	210 (47)	4 (27)	0.13
Loop diuretics, n (%)	334 (74)	13 (87)	0.27
Thiazide diuretics, n (%)	17 (4)	0	0.44
Digoxin, n (%)	93 (21)	7 (47)	0.02
Statin, n (%)	285 (63)	5 (33)	0.02
≥5 medications, n (%)	390 (86)	14 (93)	0.43
Blood tests			
NT-proBNP (ng/L)	1096 (476-2286)	3717 (2647-8715)	<0.001
Hb (g/dL)	13.1 (11.9-14.3)	11.6 (10.5-13.1)	0.004
Sodium (mmol/L)	137 (135-138)	134 (130-137)	0.02
Potassium (mmol/L)	4.4 (4.2-4.7)	4.2 (3.8-4.6)	0.07
eGFR (ml/min/1.73 m^2)	55 (40-73)	61 (32-78)	0.76

Table 9.4c: Baseline characteristics of CHF patients with ≥moderate vs <moderate malnutrition by SGA.

Malnutrition	**< Mod** N=455	**≥ Mod** N=12	**P**
Demographics			
Age (years)	76 (69-82)	79 (75-84)	0.11
Sex (male), n (%)	306 (67)	7 (58)	0.52
BP systolic (mmHg)	139 (126-162)	134 (124-136)	0.21
BP diastolic (mmHg)	75 (67-83)	69 (60-76)	0.04
HR (bpm)	70 (60-80)	75 (59-84)	0.79
Height (m)	1.69 (1.61-1.75)	1.64 (1.61-1.67)	0.06
Weight (kg)	83 (70-99)	52 (47-63)	<0.001
BMI (kg/m^2)	29.2 (25.6-33.3)	19.7 (18.2-21.9)	<0.001
NYHA III/IV, n (%)	96 (21)	7 (58)	0.002
HeFREF, n (%)	285 (63)	6 (50)	0.37
HeFNEF, n (%)	170 (37)	6 (50)	
Co-morbidities			
MI, n (%)	192 (42)	6 (50)	0.59
PVD, n (%)	69 (15)	3 (25)	0.35
HTN, n (%)	305 (67)	8 (67)	0.98
CVD, n (%)	66 (15)	5 (42)	0.01
Diabetes Mellitus, n (%)	161 (35)	2 (17)	0.18
Dementia, n (%)	42 (9)	6 (50)	<0.001
COPD, n (%)	132 (29)	8 (67)	0.005
Depression, n (%)	89 (20)	4 (33)	0.24
Anaemia, n (%)	208 (46)	10 (83)	0.01
Falls, n (%)	165 (36)	8 (67)	0.03
Urinary incontinence, n (%)	30 (7)	3 (25)	0.01
Charlson Score	8 (6-10)	10 (9-12)	0.001

Table 9.4c (continued): Baseline characteristics of CHF patients with ≥moderate vs <moderate malnutrition by SGA.

Malnutrition	< Mod	≥ Mod	P
	N=455	N=12	
Medications			
ACEi/ARB, n (%)	383 (84)	6 (50)	0.002
BB, n (%)	380 (84)	12 (100)	0.13
MRA, n (%)	210 (46)	4 (33)	0.38
Loop diuretics, n (%)	336 (74)	11 (92)	0.16
Thiazide diuretics, n (%)	17 (4)	0	0.50
Digoxin, n (%)	96 (21)	4 (33)	0.31
Statin, n (%)	286 (63)	4 (33)	0.04
≥5 medications, n (%)	392 (86)	12 (100)	0.17
Blood tests			
NT-proBNP (ng/L)	1098 (482-2309)	3750 (3634-5773)	<0.001
Hb (g/dL)	13.1 (11.9-14.2)	11.1 (10.6-12.5)	0.002
Sodium (mmol/L)	137 (135-138)	135 (133-140)	0.57
Potassium (mmol/L)	4.4 (4.2-4.7)	4.3 (3.3-4.7)	0.19
eGFR (ml/min/1.73 m^2)	55 (40-73)	63 (37-82)	0.52

Mod= moderate, HR= heart rate, BP= blood pressure, NYHA= New York Heart Association, HeFREF= heart failure with reduced ejection fraction, HeFNEF= heart failure with normal ejection fraction, BMI= body mass index, MI= myocardial infarction, PVD= peripheral vascular disease, HTN= hypertension, CVD= cerebrovascular disease, COPD= chronic obstructive pulmonary disease, BB= beta-blocker, ACEi= angiotensin converting enzyme inhibitor, ARB= angiotensin receptor blocker, MRA= mineralocorticoid receptor antagonist, NT-proBNP= N-terminal pro-B-type natriuretic peptide, Hb= haemoglobin, eGFR = estimated glomerular filtration rate, MUST = malnutrition universal screening tool, MNA-SF = mini nutritional assessment short form, SGA = subjective global assessment.

9.4.4 Detection of malnutrition: simple vs multi-dimensional tools

Malnutrition of any degree

Of the simple screening tools, GNRI had the highest, and CONUT score the lowest, agreement with multi-dimensional screening tools in identifying malnutrition of any degree (Table 9.5a). There was a greater degree of agreement in identifying patients with any degree of malnutrition using multi-dimensional screening tools compared to simple screening tools (Table 9.5b).

Table 9.5a: Agreement amongst simple vs multi-dimensional tools in identifying malnutrition (any degree).

			SIMPLE					
			CONUT		GNRI		PNI	
			NM (N=188)	M (N=279)	NM (N=378)	M (N=89)	NM (N=438)	M (N=29)
MULTI-DIMENSIONAL	MUST	NM (N=409)	38% (N=179)	49% (N=230)	77% (N=361)	10% (N=48)	85% (N=396)	3% (N=13)
		M (N=58)	2% (N=9)	11% (N=49)	4% (N=17)	9% (N=41)	9% (N=42)	3% (N=16)
			K=0.11		K=0.48		K=0.31	
	MNA-SF	NM (N=330)	34% (N=161)	37% (N=169)	66% (N=307)	5% (N=23)	69% (N=324)	1% (N=6)
		M (N=137)	6% (N=27)	23% (N=110)	15% (N=71)	14% (N=66)	25% (N=114)	5% (N=23)
			K=0.22		K=0.46		K=0.20	
	SGA	NM (N=367)	37% (N=172)	42% (N=195)	74% (N=347)	4% (N=20)	77% (N=359)	2% (N=8)
		M (N=100)	3% (N=16)	18% (N=84)	7% (N=31)	15% (N=69)	17% (N=79)	4% (N=21)
			K=0.19		K=0.66		K=0.25	

All P<0.001.

MUST= malnutrition universal screening tool, MNA-SF = mini nutritional assessment – short form, SGA= subjective global assessment, GNRI= geriatric nutritional risk index, CONUT= controlling nutritional status index, PNI= prognostic nutritional index, mal= malnourished, K= kappa coefficient, NM= non-malnourished, M= malnourished.

Table 9.5b: Agreement amongst multi-dimensional tools in identifying malnutrition (any degree).

		MUST		MNA-SF	
		NM (N=409)	M (N=58)	NM (N=330)	M (N=137)
MNA-SF	NM (N=330)	71% (N=329)	0 (N=1)	NA	
	M (N=137)	17% (N=80)	12% (N=57)		
		K=0.50			
SGA	NM (N=367)	77% (N=360)	2% (N=7)	69% (N=320)	10% (N=47)
	M (N=100)	10% (N=49)	11% (N=51)	2% (N=10)	19% (N=90)
		K=0.58		K=0.68	

All P<0.001.

MUST= malnutrition universal screening tool, MNA-SF = mini nutritional assessment – short form, SGA= subjective global assessment, K= kappa coefficient, NM= non malnourished, M= malnourished.

At least moderate malnutrition

Of the simple screening tools, GNRI had the highest, and CONUT score the lowest, agreement with multi-dimensional screening tools in identifying ≥moderate malnutrition (Table 9.6a). There was a greater degree of agreement in identifying patients with ≥moderate malnutrition using the multi-dimensional screening tools compared to simple screening tools (Table 9.6b).

Table 9.6a: Agreement amongst simple vs multi-dimensional tools in identifying malnutrition (≥moderate).

			SIMPLE					
			CONUT		GNRI		PNI	
			< Mod (N=426)	≥ Mod (N=41)	< Mod (N=438)	≥ Mod (N=29)	< Mod (N=438)	≥ Mod (N=29)
MULTI-DIMENSIONAL	MUST	< Mod (N=448)	89% (N=416)	7% (N=32)	92% (N=428)	4% (N=20)	91% (N=427)	5% (N=21)
		≥ Mod (N=19)	2% (N=10)	2% (N=9)	2% (N=10)	2% (N=9)	2% (N=11)	2% (N=8)
			K=0.26		K=0.34		K=0.30	
	MNA-SF	< Mod (N=452)	90% (N=422)	6% (N=30)	93% (N=433)	4% (N=19)	93% (N=433)	4% (N=19)
		≥ Mod (N=15)	1% (N=4)	3% (N=11)	1% (N=5)	2% (N=10)	1% (N=5)	2% (N=10)
			K=0.36		K=0.43		K=0.43	
	SGA	< Mod (N=455)	90% (N=422)	7% (N=33)	93% (N=434)	4% (N=21)	93% (N=433)	5% (N=22)
		≥ Mod (N=12)	1% (N=4)	2% (N=8)	1% (N=4)	2% (N=8)	1% (N=5)	1% (N=7)
			K=0.27		K=0.37		K=0.32	

All P<0.001.

MUST= malnutrition universal screening tool, MNA-SF = mini nutritional assessment – short form, SGA= subjective global assessment, GNRI= geriatric nutritional risk index, CONUT= controlling nutritional status index, PNI= prognostic nutritional index, mal= malnourished, K= kappa coefficient, Mod= moderate malnutrition.

Table 9.6b: Agreement amongst multi-dimensional tools in identifying malnutrition (≥moderate).

		MUST		MNA-SF	
		< Mod (N=448)	≥ Mod (N=19)	< Mod (N=452)	≥ Mod (N=15)
MNA-SF	< Mod (N=452)	94% (N=441)	2% (N=11)	NA	
	≥ Mod (N=15)	2% (N=7)	2% (N=8)		
		K=0.45			
SGA	< Mod (N=455)	95% (N=445)	2% (N=10)	96% (N=448)	1.5% (N=7)
	≥ Mod (N=12)	1% (N=3)	2% (N=9)	1% (N=4)	1.5% (N=8)
		K=0.57		K=0.58	

All P<0.001.

MUST= malnutrition universal screening tool, MNA-SF = mini nutritional assessment – short form, SGA= subjective global assessment, K= kappa coefficient, Mod= moderate malnutrition.

9.4.5 Malnutrition tools vs combined index

Malnutrition of any degree

Amongst patients with CHF, MNA-SF had the greatest sensitivity while MUST and PNI had the highest specificity in identifying malnutrition of any degree defined by the combined index (Tables 9.7a-c). SGA had the lowest, and CONUT score had the highest misclassification rate. Laboratory tests generally had higher misclassification rates compared to either simple or multi-dimensional screening tools.

Table 9.7a: Performance of simple tools in identifying malnutrition (any degree) according to the combined index.

	Simple		
	CONUT >1	GNRI ≤ 98	PNI ≤38
Sensitivity (%)	84	65	20
Specificity (%)	45	92	98
PPV (%)	23	69	69
NPV (%)	94	91	82
False positive (%)	46	6	2
False negative (%)	3	7	17
Misclassification rate (%)	49	13	19

Table 9.7b: Performance of multi-dimensional tools in identifying malnutrition (any degree) according to the combined index.

	Multi-dimensional		
	MUST ≥ 1	MNA-SF <12	SGA B/C
Sensitivity (%)	51	93	88
Specificity (%)	98	83	92
PPV (%)	84	51	69
NPV (%)	89	98	98
False positive (%)	2	14	7
False negative (%)	10	1	2
Misclassification rate (%)	12	15	9

Table 9.7c: Performance of laboratory tests in identifying malnutrition (any degree) according to the combined index.

	Laboratory tests		
	Lymphocyte* <1.6x10^9/L	**Albumin*** <35 g/L	**Cholesterol*** <4.6 mmol/L
Sensitivity (%)	70	56	70
Specificity (%)	62	83	42
PPV (%)	26	47	19
NPV (%)	91	88	88
False positive (%)	32	13	49
False negative (%)	5	9	5
Misclassification rate (%)	37	22	54

*cut-off according to CONUT score.

GNRI= geriatric nutritional risk index, CONUT= controlling nutritional status index, PNI= prognostic nutritional index, MUST= malnutrition universal screening tool, MNA-SF = mini nutritional assessment – short form, SGA= subjective global assessment, PPV= positive predictive value, NPV= negative predictive value.

In non-obese patients (BMI<30 kg/m^2), GNRI had a sensitivity of 73% in identifying malnutrition of any degree, but its sensitivity was zero in obese patients (BMI≥30 kg/m^2) (Tables 9.8a-b).

Table 9.8a: Performance of simple tools in identifying malnutrition (any degree) in non-obese patients according to the combined index.

	Simple		
	CONUT >1	GNRI ≤ 98	PNI ≤38
Sensitivity (%)	84	73	21
Specificity (%)	44	85	98
PPV (%)	36	69	86
NPV (%)	88	88	71
False positive (%)	41	10	1
False negative (%)	5	8	26
Misclassification rate (%)	46	18	27

Table 9.8b: Performance of simple tools in identifying malnutrition (any degree) in obese patients according to the combined index.

	Simple		
	CONUT >1	GNRI ≤ 98	PNI ≤38
Sensitivity (%)	100	0	11
Specificity (%)	46	100	97
PPV (%)	3	100	14
NPV (%)	100	94	96
False positive (%)	53	0	3
False negative (%)	0	6	4
Misclassification rate (%)	53	6	7

GNRI= geriatric nutritional risk index, CONUT= controlling nutritional status index, PNI= prognostic nutritional index, PPV= positive predictive value, NPV= negative predictive value.

Similarly, in non-obese patients, SGA had a sensitivity of 94% in identifying malnutrition of any degree, but its sensitivity was 38% in obese patients (Tables 9.9a-b).

Table 9.9a: Performance of multi-dimensional tools in identifying malnutrition (any degree) in non-obese patients according to the combined index.

	Multi-dimensional		
	MUST ≥ 1	MNA-SF <12	SGA B/C
Sensitivity (%)	52	93	94
Specificity (%)	97	84	86
PPV (%)	88	68	70
NPV (%)	81	97	98
False positive (%)	2	12	10
False negative (%)	16	2	2
Misclassification rate (%)	18	14	12

Table 9.9b: Performance of multi-dimensional tools in identifying malnutrition (any degree) in obese patients according to the combined index.

	Multi-dimensional		
	MUST ≥ 1	MNA-SF <12	SGA B/C
Sensitivity (%)	38	100	38
Specificity (%)	98	82	98
PPV (%)	50	8	50
NPV (%)	97	100	97
False positive (%)	2	18	2
False negative (%)	3	0	3
Misclassification rate (%)	5	18	5

MUST= malnutrition universal screening tool, MNA-SF = mini nutritional assessment – short form, SGA= subjective global assessment, PPV= positive predictive value, NPV= negative predictive value.

Single laboratory tests have similar classification performance in non-obese versus obese patients (Tables 9.10a-b).

Table 9.10a: Performance of laboratory tests in identifying malnutrition (any degree) in non-obese patients according to the combined index.

	Laboratory tests		
	Lymphocyte* <1.6x10^9/L	**Albumin*** <35 g/L	**Cholesterol*** <4.6 mmol/L
Sensitivity (%)	70	55	70
Specificity (%)	60	87	42
PPV (%)	39	68	31
NPV (%)	84	80	79
False positive (%)	29	9	42
False negative (%)	8	15	8
Misclassification rate (%)	37	24	50

Table 9.10b: Performance of laboratory tests in identifying malnutrition (any degree) in obese patients according to the combined index.

	Laboratory tests		
	Lymphocyte* <1.6x10^9/L	**Albumin*** <35 g/L	**Cholesterol*** <4.6 mmol/L
Sensitivity (%)	67	67	67
Specificity (%)	64	79	42
PPV (%)	3	13	2
NPV (%)	99	98	99
False positive (%)	36	20	57
False negative (%)	1	2	1
Misclassification rate (%)	37	22	58

*cut-off according to CONUT score.

PPV= positive predictive value, NPV= negative predictive value.

At least moderate malnutrition

Amongst patients with CHF, CONUT score had the greatest sensitivity while MNA-SF and SGA had the highest specificity in identifying ≥moderate malnutrition defined by the combined index (Table 9.11a-c). MNA-SF had the lowest, and CONUT score the highest misclassification rate. Laboratory tests generally had higher misclassification rates compared to either simple or multi-dimensional screening tools.

Table 9.11a: Performance of simple tools in identifying malnutrition (≥moderate) according to the combined index.

	Simple		
	CONUT >4	GNRI <92	PNI ≤38
Sensitivity (%)	80	57	73
Specificity (%)	94	95	96
PPV (%)	29	28	38
NPV (%)	99	99	99
False positive (%)	6	5	4
False negative (%)	1	1	1
Misclassification rate (%)	7	6	5

Table 9.11b: Performance of multi-dimensional tools in identifying malnutrition (≥moderate) according to the combined index.

	Multi-dimensional		
	MUST ≥ 2	MNA-SF ≤7	SGA C
Sensitivity (%)	56	69	56
Specificity (%)	98	99	99
PPV (%)	47	73	75
NPV (%)	98	99	98
False positive (%)	2	1	1
False negative (%)	2	1	2
Misclassification rate (%)	4	2	3

Table 9.11c: Performance of laboratory tests in identifying malnutrition (≥moderate) according to the combined index.

	Laboratory tests		
	Lymphocyte* <1.2x10^9/L	**Albumin*** <30 g/L	**Cholesterol*** <3.62 mmol/L
Sensitivity (%)	56	38	60
Specificity (%)	84	98	68
PPV (%)	7	42	6
NPV (%)	99	98	98
False positive (%)	15	2	31
False negative (%)	1	2	1
Misclassification rate (%)	16	4	32

*cut-off according to CONUT score. PPV= positive predictive value, NPV= negative predictive value.

GNRI= geriatric nutritional risk index, CONUT= controlling nutritional status index, PNI= prognostic nutritional index, MUST= malnutrition universal screening tool, MNA-SF = mini nutritional assessment – short form, SGA= subjective global assessment, PPV= positive predictive value, NPV= negative predictive value.

In non-obese patients (BMI<30 kg/m^2), GNRI had a sensitivity of 62% in identifying ≥moderate malnutrition, but its sensitivity was zero in obese patients (BMI≥30 kg/m^2) (Table 9.12a-b).

Table 9.12a: Performance of simple tools in identifying malnutrition (≥moderate) in non-obese patients according to the combined index.

	Simple		
	CONUT >4	GNRI <92	PNI ≤38
Sensitivity (%)	79	62	71
Specificity (%)	92	92	95
PPV (%)	34	28	45
NPV (%)	99	98	98
False positive (%)	8	8	5
False negative (%)	1	2	2
Misclassification rate (%)	9	10	7

Table 9.12b: Performance of simple tools in identifying malnutrition (≥moderate) in obese patients according to the combined index.

	Simple		
	CONUT >4	GNRI <92	PNI ≤38
Sensitivity (%)	100	0	100
Specificity (%)	96	100	97
PPV (%)	11	100	14
NPV (%)	100	99	100
False positive (%)	4	0	3
False negative (%)	0	1	0
Misclassification rate (%)	4	1	3

GNRI= geriatric nutritional risk index, CONUT= controlling nutritional status index, PNI= prognostic nutritional index, PPV= positive predictive value, NPV= negative predictive value.

Similarly, in non-obese patients, SGA had a sensitivity of 60% in identifying ≥moderate malnutrition, but its sensitivity was zero in obese patients (Table 9.13a-b).

Table 9.13a: Performance of multi-dimensional tools in identifying malnutrition (≥moderate) in non-obese patients according to the combined index.

	Multi-dimensional		
	MUST ≥ 2	MNA-SF ≤7	SGA C
Sensitivity (%)	53	67	60
Specificity (%)	96	99	99
PPV (%)	47	77	75
NPV (%)	97	98	98
False positive (%)	3	1	1
False negative (%)	3	2	2
Misclassification rate (%)	6	3	3

Table 9.13b: Performance of multi-dimensional tools in identifying malnutrition (≥moderate) in obese patients according to the combined index.

	Multi-dimensional		
	MUST ≥ 2	MNA-SF ≤7	SGA C
Sensitivity (%)	100	100	0
Specificity (%)	99	99	100
PPV (%)	50	50	100
NPV (%)	100	100	99
False positive (%)	1	1	0
False negative (%)	0	0	1
Misclassification rate (%)	1	1	1

MUST= malnutrition universal screening tool, MNA-SF = mini nutritional assessment – short form, SGA= subjective global assessment, PPV= positive predictive value, NPV= negative predictive value.

In non-obese patients, serum cholesterol of <3.62 mmol/L had a 64% sensitivity in identifying ≥moderate malnutrition, but its sensitivity was zero in obese patients (Tables 9.14a-b).

Table 9.14a: Performance of laboratory tests in identifying malnutrition (≥moderate) in non-obese patients according to the combined index.

	Laboratory tests		
	Lymphocyte* <1.2x10^9/L	**Albumin*** <30 g/L	**Cholesterol*** <3.62 mmol/L
Sensitivity (%)	56	33	64
Specificity (%)	80	98	67
PPV (%)	9	50	10
NPV (%)	98	97	97
False positive (%)	20	1	31
False negative (%)	1	3	2
Misclassification rate (%)	21	4	33

Table 9.14b: Performance of laboratory tests in identifying malnutrition (≥moderate) in obese patients according to the combined index.

	Laboratory tests		
	Lymphocyte* <1.2x10^9/L	**Albumin*** <30 g/L	**Cholesterol*** <3.62 mmol/L
Sensitivity (%)	100	100	0
Specificity (%)	91	98	69
PPV (%)	0	25	0
NPV (%)	100	100	99
False positive (%)	9	2	31
False negative (%)	0	0	1
Misclassification rate (%)	9	2	32

*cut-off according to CONUT score. PPV= positive predictive value, NPV= negative predictive value.

9.4.6 Inter-operator agreement of SGA

There was a substantial agreement between the two operators' judgement on the degree of malnutrition in a random sample of patients (N=23) using the SGA, with a Kappa coefficient (K) of 0.65 (95% CI: 0.59-0.71, P=0.001).

9.4.7 Time needed to complete malnutrition evaluation

Malnutrition screening using simple tools on average took no more than 1 minute to complete, whereas multi-dimensional assessment using the SGA on average took 20 minutes to complete.

9.5 Discussion

This study is the first to directly compare several commonly used simple vs multi-dimensional malnutrition tools in patients with CHF. The main finding is that malnutrition was common in this population. The prevalence of any degree and ≥moderate malnutrition was 6-60% and 3-9%, respectively, depending on the tool used. These findings are similar to those from a recent meta-analysis which studied the role of different malnutrition tools in patients with HF (118). Lin and colleagues reported the prevalence of malnutrition to vary between 16-62%, depending on the malnutrition tool used and the population studied (118).

Our results showed that there was a much greater variation in the prevalence of malnutrition (any degree and ≥moderate) amongst simple tools (any degree: 6-60%; ≥moderate: 6-9%) compared to multi-dimensional tools (any degree: 12-29%; ≥moderate: 3-4%). The CONUT score in particular suggested that many more patients were 'malnourished' compared to GNRI or PNI. There was a greater degree of agreement in identifying malnourished patients using multi-dimensional tools compared to simple tools. The agreement between simple and multi-dimensional tools was weak for some tools, suggesting that the tools are measuring different aspects of malnutrition as they do not identify the same group of patients as being malnourished. The heterogeneity of the tools was further demonstrated by our finding that the prevalence of malnutrition was higher in patients with AF than in those with SR according to some malnutrition tools but not others.

We found that malnutrition was equally common in patients with HeFREF and in those with HeFNEF. Malnutrition was more common in patients with worse NYHA classes and higher natriuretic peptide levels, suggesting that malnutrition is more closely related to the severity of HF rather than to the HF phenotype.

Different tools have their own strengths and weaknesses. Amongst the simple screening tools, CONUT score has the highest sensitivity, but it also has the highest false positive rate compared with the combined index. CONUT score is confounded by the use of statins (62% of patients with CHF were on statins), which causes lower cholesterol levels irrespective of nutritional status. Furthermore, of the 3 components of CONUT score,

serum cholesterol level and total lymphocyte count treated as single measures misclassified a significant proportion of patients compared with the combined index. Therefore, CONUT score might not be the best tool to identify malnutrition in patients with CHF.

PNI (although specific) has the highest false negative rate in identifying malnutrition of any degree, hence underestimating malnutrition compared to other tools. This is because PNI does not have a mild malnutrition category and only identifies patients with ≥moderate malnutrition. GNRI seems to be the best simple screening tool for malnutrition in patients with CHF, but only when BMI is <30 kg/m^2.

The multi-dimensional tools offer a more comprehensive evaluation of nutritional status compared to the simple tools. MUST score and MNA are both commonly used in different settings including hospital wards, clinics, general practice and care homes (186, 187). MNA-SF, a shorter version of MNA, is quicker to complete and has similar validity and accuracy as the MNA in detecting malnutrition in older adults (188). In this study, amongst all the tools studied, MNA-SF had the lowest misclassification rate in detecting significant malnutrition compared with the combined index, therefore might be a useful malnutrition tool to apply in patients with CHF. Compared to MUST, apart from considering BMI, weight loss and the effect of acute illness on nutritional intake, MNA-SF also evaluates mobility and neuropsychological problems.

SGA is the most comprehensive of the 3 multi-dimensional screening tools. It considers weight change, dietary changes, gastrointestinal symptoms, functional capacity and the results of a comprehensive physical examination. Similar to MNA-SF, SGA also has a low misclassification rate in detecting significant malnutrition compared with the combined index. However, SGA is subjective and is not sensitive in detecting malnutrition in obese patients. It also requires significant time to perform (on average 20 minutes).

Biomarkers such as total lymphocyte count, albumin and cholesterol have long been used in isolation to evaluate nutritional status, but they might be affected by treatments, social conditions, or other diseases rather than malnutrition alone. Therefore, they are unlikely to be able to evaluate nutritional status accurately (189). In this study, individual

biomarkers apart from albumin, had significantly higher misclassification rates than simple and multi-dimensional tools.

9.6 Study limitations

Firstly, this study is a single-centre study with limited sample size, which mainly enrolled Caucasians. External validation of our results in other populations is needed. This study is, however, the largest study which compared the agreement and classification performance of several commonly used malnutrition tools in consecutive, unselected patients with CHF.

Secondly, I have only studied 6 of the most commonly used malnutrition tools in literature. A large number of other malnutrition tools have been proposed and identified patients at risk of adverse outcomes in other clinical scenarios (118).

Thirdly, this study only focused on investigating the prevalence of malnutrition using different tools. Further studies are needed to explore the prognostic significance of these tools and establish which tool(s) is/ are the best to use in patients with CHF.

9.7 Conclusion

Malnutrition is common in patients with CHF. Its prevalence is variable depending on the malnutrition tool used. Amongst the tools studied, MNA-SF has the best classification performance in identifying significant malnutrition compared with the combined index. The next chapter will explore whether single laboratory tests or simple malnutrition tools have comparable prognostic significance to more comprehensive multi-dimensional tools.

Chapter 10 Prognostic Significance of Malnutrition Tools in Patients with Chronic Heart Failure

10.1 Chapter summary

Background: Malnutrition is common in patients with CHF and is associated with adverse outcomes, but it is uncertain how malnutrition should best be evaluated.

Objectives: To compare the prognostic significance of several commonly used malnutrition tools in ambulatory patients with CHF.

Methods: I evaluated malnutrition, simultaneously using 3 simple tools (COntroling NUTritional Status (CONUT) score; Geriatric nutritional risk index (GNRI); and Prognostic nutritional index (PNI)), 3 multi-dimensional tools (Malnutrition universal screening tool (MUST); Mini nutritional assessment-short form (MNA-SF); and Subjective global assessment (SGA)) and 3 laboratory tests (serum cholesterol, albumin and total lymphocyte count) in consecutive patients with CHF attending a routine follow-up visit.

Results: I studied 467 patients (67% male, median (IQR) age 76 (69-82) years, median (IQR) NT-proBNP 1156 (469-2463) ng/L). During a median follow-up of 554 (IQR: 511-629) days, 82 patients died and 201 patients were either hospitalised or died.

In models corrected for age, NYHA class, log [NT-proBNP], Charlson score, Hb, eGFR and AF, all malnutrition tools (as continuous variables) except total lymphocyte count, were significant predictors of all-cause mortality.

A base model for predicting mortality including NYHA class, log [NT-proBNP] and AF, had a Harrell's C-statistic of 0.71. Amongst simple tools: CONUT score (C-statistic=0.76); amongst multi-dimensional tools: MNA-SF (C-statistic=0.75) and amongst laboratory tests: albumin (C-statistic=0.75), all as continuous variables, increased model performance most compared to base model ($P<0.05$ for all).

Conclusion: Malnutrition is strongly associated with increased mortality in ambulatory patients with CHF. Measuring serum albumin provides comparable prognostic information to simple or multi-dimensional malnutrition tools.

10.2 Introduction

Malnutrition is highly prevalent in patients with HF and is associated with significant disability, morbidity and mortality (118). The relationship between malnutrition and HF is complex. On one hand, nutritional deficiencies might cause atrophy and fibrosis of cardiac myocytes, leading to reduced LV mass and function (190, 191). The lack of nutrients secondary to poor lifestyles and habits such as chronic and severe alcoholism, might also contribute to the development of overt HF. On the other hand, HF itself predisposes to congestive enteropathy and malabsorption (92). The sustained neurohormonal activation and chronic inflammation associated with HF lead to hypercatabolism, which, in turn, predisposes to sarcopenia and cachexia (111). Older age, polypharmacy, and other co-morbidities, such as dementia or frailty (192), might further increase the risk of malnutrition in patients with HF.

Current guidelines recommend assessment of nutritional status in patients with HF (5), but there is no consensus as to how malnutrition should best be measured. In Chapter 9, I have studied in detail the agreement and classification performance of several commonly used malnutrition tools. In this chapter, I will compare the prognostic significance of these tools in a cohort of well-characterised ambulatory patients with CHF.

10.3 Methods

10.3.1 Study population

I prospectively recruited 467 consecutive ambulatory patients with CHF who attended our community HF clinic at Castle Hill Hospital, Hull, UK between September 2016 and March 2017. All patients had a pre-existing (>1 year) clinical diagnosis of CHF. Details of the study population has been described in the 'methods' section of Chapter 7.

10.3.2 Malnutrition evaluation

I evaluated malnutrition in patients with CHF using the following tools:

- Simple screening tools:
    1. COntroling NUTritional Status (CONUT) score
    2. Geriatric nutritional risk index (GNRI)
    3. Prognostic nutritional index (PNI)
- Multi-dimensional tools:
    1. Malnutrition universal screening tool (MUST)
    2. Mini nutritional assessment-short form (MNA-SF)
    3. Subjective global assessment (SGA)
- Laboratory tests:
    1. Serum total cholesterol
    2. Serum albumin level
    3. Serum total lymphocyte count

The entire malnutrition evaluation process took an hour per patient. A description of the malnutrition evaluation process can be found in the ‘malnutrition evaluation’ section in Chapter 4.

10.3.3 Body composition analysis

A subset of patients (N=233), who provided informed consent, had further body composition analysis. Patients who had poor mobility, severe symptoms and pacemakers or defibrillators were excluded. Body composition assessment was performed using Tanita MC-180 MA scales (Tanita Europe BV, the Netherlands). A description of the body composition evaluation process can be found in the ‘body composition analysis’ section of Chapter 4.

10.3.4 End points and follow up

I followed the patients until 1st of August 2018. All patients were followed for a minimum of 1 year. The primary end point was all-cause mortality and the secondary end point was the combination of all-cause hospitalisation and all-cause mortality. The handling of data regarding mortality and hospitalisation can be found in the 'end points and follow up section' in Chapter 4.

10.3.5 Statistical analysis

Routine statistical analyses have been detailed in Chapter 4.

I studied the prognostic significance of different malnutrition tools using several steps. Firstly, I performed univariable analysis with Cox proportional hazard regression to determine significant predictors of events. Then, I entered the clinical variables with $P<0.05$ in univariable analysis into multivariable models with each malnutrition tool both as a continuous and a binary variable. Next, I created a base model including NYHA (III/IV vs I/II), log [NT-proBNP] and cardiac rhythm (AF vs SR) for predicting mortality. I excluded BMI and co-morbidities (such as anaemia and renal dysfunction) from the model as some of the malnutrition tools take into account these variables. I added each of the malnutrition tools in turn to the base model and used Harrell's C-statistic to evaluate model discrimination in survival analysis. Furthermore, I constructed Kaplan-Meier curves to present time-to-event data. Finally, I performed further analyses to study the relationship between the degree of malnutrition and outcome. I used the malnutrition tool from each category (simple tools, multi-dimensional tools and laboratory tests) which best predicted all-cause mortality (highest χ^2).

To evaluate the length of stay during hospitalisation, I only included patients with ≥1 hospitalisation and hospitalisations resulting in death were excluded.

10.4 Results

10.4.1 Baseline characteristics

A total of 467 consecutive ambulatory patients with CHF was studied. The baseline characteristics of CHF patients have been shown in Table 7.1. The baseline characteristics of CHF patients who survived at 1 year follow up vs those who did not have been shown in Table 8.1. Compared to patients who were alive at 1 year, those who died were more likely to be malnourished at baseline (Table 10.1).

Table 10.1: Prevalence of malnutrition in CHF patients (died by 1 year vs alive at 1 year).

	Died at 1 year N=56	**Alive at 1 year** N=411	**P**
Malnutrition tools			
CONUT (mal)	52 (93)	227 (55)	<0.001
GNRI (mal)	20 (36)	69 (17)	0.001
PNI (mal)*	8 (14)	21 (5)	0.008
MUST (mal)	17 (30)	41 (10)	<0.001
MNA-SF (mal)	37 (66)	100 (24)	<0.001
SGA (mal)	30 (54)	70 (17)	<0.001
Cholesterol (mal)	40 (71)	242 (59)	0.07
Albumin (mal)	33 (59)	83 (20)	<0.001
Lymphocyte (mal)	35 (63)	168 (41)	0.002

Mal= malnourished, CONUT = Controlling nutritional status score, GNRI = geriatric nutritional risk index, PNI = prognostic nutritional index, MUST= malnutrition universal screening tool, MNA-SF= mini nutritional assessment-short form, SGA = subjective global assessment.

*moderate malnutrition vs no malnutrition (PNI classifies patients as non-malnourished, moderately or severely malnourished)

10.4.2 Relation between malnutrition and mortality

During a median follow-up of 554 days (IQR: 511-629 days), 18% of patients died. The influence of malnutrition measures considered as univariable predictors of mortality is

shown in Table 10.2. Univariable analysis of clinical factors predicting mortality has been shown in Table 8.2b. The presence of malnutrition, as determined by any tool, except serum cholesterol (when used as a binary variable), was associated with an increased risk of mortality.

Table 10.2: Univariable analysis of malnutrition tools predicting all-cause mortality.

Worse outcome per unitary increase		**HR (95%CI)**	**χ^2**	**P**
Laboratory tests	Albumin (g/L)	0.82 (0.77-0.87)	46.2	<0.001
	Albumin (Mal vs not mal)	3.14 (2.03-4.85)	26.6	<0.001
	Cholesterol (mmol/L)	0.66 (0.53-0.83)	12.7	<0.001
	Cholesterol (Mal vs not mal)	1.60 (0.99-2.59)	3.6	0.06
	Lymphocyte ($x10^9$/L)	0.50 (0.34-0.74)	11.7	0.001
	Lymphocyte (Mal vs not mal)	1.80 (1.16-2.78)	7.0	0.008
Simple	CONUT	1.45 (1.31-1.60)	53.9	<0.001
	CONUT (Mal vs not mal)	4.98 (2.64-9.40)	24.5	<0.001
	GNRI	0.96 (0.94-0.97)	24.4	<0.001
	GNRI (Mal vs not mal)	2.35 (1.48-3.72)	13.1	<0.001
	PNI	0.86 (0.83-0.90)	44.1	<0.001
	PNI (Mal vs not mal)*	3.35 (1.85-6.07)	16.0	<0.001
Multi-dimensional	MUST	1.84 (1.48-2.30)	29.3	<0.001
	MUST (Mal vs not mal)	3.15 (1.95-5.10)	21.8	<0.001
	MNA-SF	0.74 (0.68-0.80)	53.5	<0.001
	MNA-SF (Mal vs not mal)	4.28 (2.75-6.65)	41.5	<0.001
	SGA	3.06 (2.25-4.16)	51.1	<0.001
	SGA (Mal vs not mal)	4.26 (2.76-6.58)	43.0	<0.001

Mal= malnourished, CONUT = Controlling nutritional status score, GNRI = geriatric nutritional risk index, PNI = prognostic nutritional index, MUST= malnutrition universal screening tool, MNA-SF= mini nutritional assessment –short form, SGA = subjective global assessment.

*moderate malnutrition vs no malnutrition (PNI classifies patients as non-malnourished, moderately or severely malnourished)

Clinical variables included in multivariable analyses for predicting mortality are shown in Table 10.3a. All malnutrition tools, with the exception of total lymphocyte count, and

GNRI, PNI and MUST as binary variables, were significant predictors of all-cause mortality when evaluated individually in multivariable analysis (Table 10.3b).

Amongst the multi-dimensional tools, MNA-SF best predicted all-cause mortality (highest χ^2 in multivariable analysis). Therefore, I performed additional analyses to study the prognostic value of individual components of MNA-SF. All components of MNA-SF, except BMI, were significant univariable predictors of mortality (Table 10.4a). In a multivariable model including clinical variables in Table 10.3a, amongst the components of MNA-SF, only worsening mobility was a significant predictor of mortality (Table 10.4b).

A base model including NYHA (III/IV vs I/II), log [NT-proBNP] and cardiac rhythm (AF vs SR) for predicting mortality achieved a Harrell's C-statistic of 0.71 (Table 10.5). Each malnutrition tool, when added individually, improved performance of the base model. Amongst simple tools: CONUT score (C-statistics=0.76); amongst multi-dimensional tools: MNA-SF (C-statistics=0.75); and amongst laboratory tests: albumin (C-statistics=0.75), all as continuous variables, increased model performance most compared with the base model (all P<0.05).

Table 10.3a: Clinical variables included in multivariable analyses for predicting all-cause mortality. (using CONUT as an example)

Worse outcome per unitary increase	**HR (95%CI)**	**χ^2**	**P**
Age (years)	1.00 (0.97-1.04)	0.05	0.83
BMI (kg/m^2)	0.99 (0.94-1.03)	0.51	0.47
Rhythm (AF vs SR)	1.26 (0.77-2.06)	0.82	0.37
NYHA (III/IV vs I/II)	1.20 (0.72-2.00)	0.48	0.49
Charlson Score	1.19 (1.06-1.34)	8.48	0.004
Log [NT-proBNP]	2.27 (1.21-4.27)	6.45	0.01
Hb (g/L)	0.99 (0.98-1.01)	0.62	0.43
eGFR (mL/min per 1.73 m^2)	0.99 (0.98-1.01)	1.25	0.26
CONUT	**1.28 (1.13-1.45)**	**15.42**	**<0.001**

HR = hazard ratio, CI= confidence interval, χ^2= chi-square, BMI= body mass index, AF= atrial fibrillation, SR= sinus rhythm, NYHA= New York Heart Association, NT-proBNP= N-terminal pro-B-type natriuretic peptide, Hb= haemoglobin, eGFR = estimated glomerular filtration rate, CONUT = Controlling nutritional status score.

Table 10.3b: Multivariable analysis of malnutrition tools predicting all-cause mortality. (Separate multivariable analysis was performed for each tool as both a binary and a continuous variable, with Table 10.3a showing the clinical variables included in multivariable analyses for predicting all-cause mortality)

Worse outcome per unitary increase		HR (95%CI)	χ^2	P
Laboratory tests	Albumin (g/L)	0.87 (0.81-0.93)	14.7	<0.001
	Albumin (Mal vs not mal)	2.05 (1.28-3.28)	9.0	0.003
	Cholesterol (mmol/L)	0.72 (0.58-0.90)	8.0	0.005
	Cholesterol (Mal vs not mal)	1.64 (1.00-2.69)	3.9	0.05
	Lymphocyte ($x10^9$/L)	0.89 (0.61-1.30)	0.4	0.55
	Lymphocyte (Mal vs not mal)	0.99 (0.62-1.58)	0.001	0.97
Simple	CONUT	1.28 (1.13-1.45)	15.4	<0.001
	CONUT (Mal vs not mal)	3.05 (1.58-5.85)	11.2	0.001
	GNRI	0.98 (0.96-1.00)	4.9	0.03
	GNRI (Mal vs not mal)	1.18 (0.69-2.02)	0.4	0.55
	PNI	0.92 (0.88-0.98)	8.4	0.004
	PNI (Mal vs not mal)*	1.45 (0.73-2.88)	1.1	0.29
Multi-dimensional	MUST	1.38 (1.03-1.84)	4.6	0.03
	MUST (Mal vs not mal)	1.32 (0.74-2.33)	0.9	0.35
	MNA-SF	0.84 (0.75-0.93)	10.2	0.001
	MNA-SF (Mal vs not mal)	2.09 (1.26-3.47)	8.2	0.004
	SGA	1.83 (1.12-3.00)	5.8	0.02
	SGA (Mal vs not mal)	2.06 (1.10-3.88)	5.1	0.03

Variables in multivariable analysis predicting all-cause mortality included: Age, BMI, AF vs SR, NYHA (III/IV vs I/II), Charlson score, log[NT-proBNP], Hb, eGFR. (BMI is not included in multivariable analyses involving MNA-SF, GNRI or MUST as it is part of these scores).

*moderate malnutrition vs no malnutrition (PNI classifies patients as non-malnourished, moderately or severely malnourished)

Mal= malnourished, CONUT = Controlling nutritional status score, GNRI = geriatric nutritional risk index, PNI = prognostic nutritional index, MUST= malnutrition universal screening tool, MNA-SF= mini nutritional assessment –short form, SGA = subjective global assessment.

Table 10.4a: Univariable analysis of components of MNA-SF predicting all-cause mortality.

Worse outcome	HR (95%CI)	χ^2	P
Decline in food intake (per categorical increase)	1.47 (1.00-2.17)	3.9	0.04
Weight loss during last 3 months (per categorical increase)	1.66 (1.36-2.03)	24.5	<0.001
Mobility (per categorical decrease)	3.94 (2.83-5.49)	65.5	<0.001
Psychological stress/ acute disease during last 3 months (yes vs no)	2.48 (1.56-3.93)	14.9	<0.001
Neuropsychological problems (per categorical increase)	1.80 (1.19-2.71)	7.9	0.005
BMI (per categorical decrease)	1.27 (0.94-1.71)	2.4	0.12

Table 10.4b: Multivariable analysis of components of MNA-SF predicting all-cause mortality.

Worse outcome	HR (95%CI)	χ^2	P
Age (years)	1.01 (0.99-1.04)	0.8	0.36
Rhythm (AF vs SR)	1.24 (0.76-2.03)	0.7	0.39
NYHA (III/IV vs I/II)	1.07 (0.65-1.76)	0.1	0.80
Log [NT-proBNP]	2.47 (1.35-4.49)	8.7	0.003
Hb (g/L)	0.99 (0.98-1.01)	1.7	0.20
eGFR (mL/min per 1.73 m^2)	0.99 (0.97-1.00)	4.4	0.04
Decline in food intake (per categorical increase)	1.02 (0.67-1.54)	0.01	0.93
Weight loss during last 3 months (per categorical increase)	1.18 (0.94-1.50)	2.0	0.16
Mobility (per categorical decrease)	2.59 (1.75-3.82)	22.8	<0.001
Psychological stress/ acute disease during last 3 months (yes vs no)	1.38 (0.87-2.17)	1.9	0.17
Neuropsychological problems (per categorical increase)	1.07 (0.63-1.81)	0.1	0.81

Charlson score not included as MNA-SF takes into account neuropsychological problems which forms part of Charlson score

HR = hazard ratio, CI= confidence interval, χ^2= chi-square, AF= atrial fibrillation, SR= sinus rhythm, NYHA= New York Heart Association, NT-proBNP= N-terminal pro-B-type natriuretic peptide, Hb= haemoglobin, eGFR = estimated glomerular filtration rate, BMI= body mass index.

Table 10.5: Addition of malnutrition tools and its impact on performance of base model in predicting all-cause mortality.

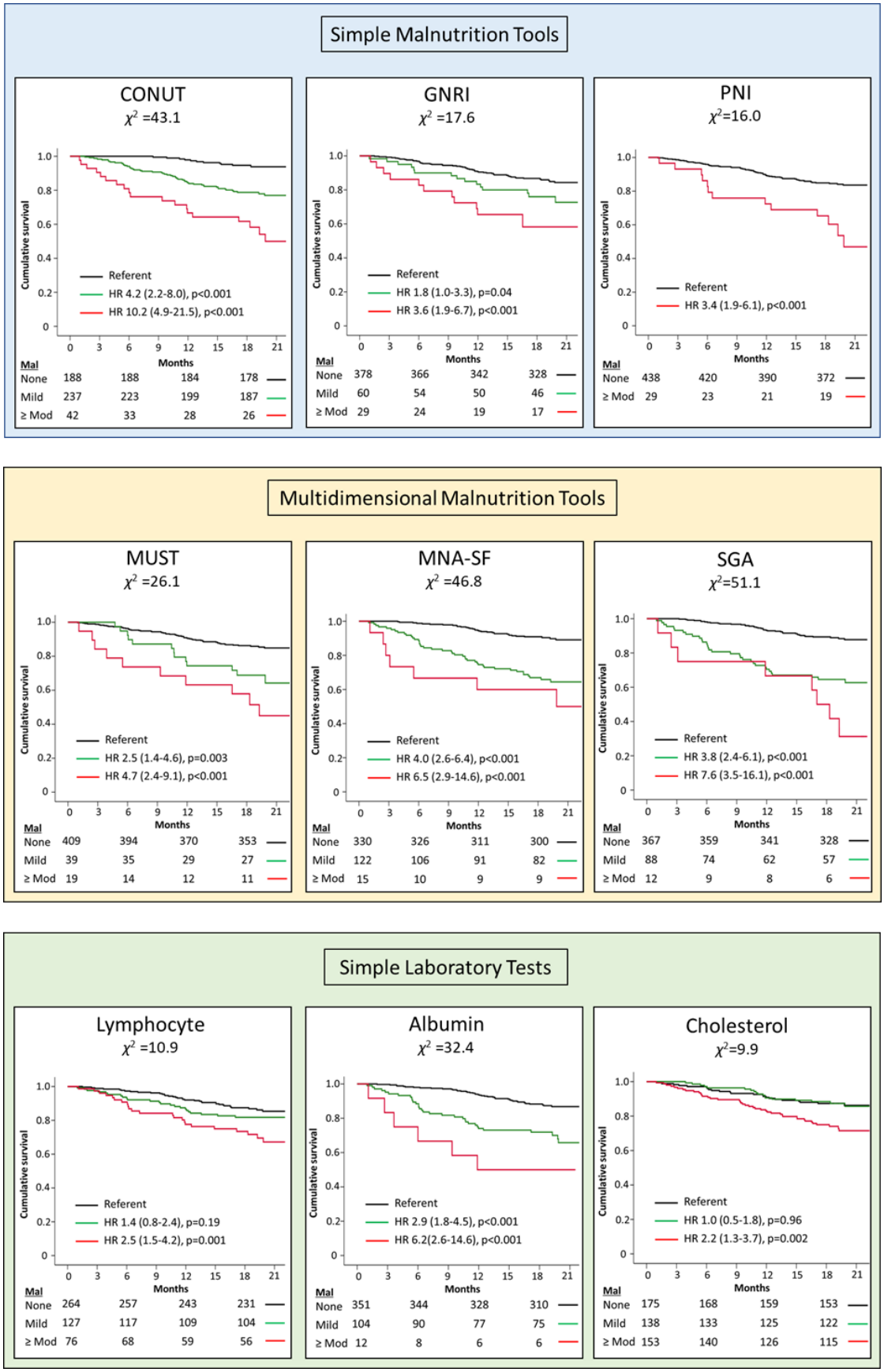
Model	Harrell's C-statistics (95% CI)	Difference
Base model*	0.71 (0.66-0.77)	Compared to base model (t-statistic, P)
Base* + BMI	0.73 (0.67-0.78)	t = 1.69, P = 0.09
Screening tools		
Base* + CONUT	0.76 (0.71-0.81)	t = 3.01, P = 0.003
Base* + GNRI	0.74 (0.69-0.80)	t = 2.04, P = 0.04
Base* + PNI	0.75 (0.69-0.80)	t = 2.21, P = 0.03
Multi-dimensional tools		
Base* + MUST	0.73 (0.67-0.78)	t = 1.42, P = 0.16
Base* + MNA-SF	0.75 (0.70-0.81)	t = 2.58, P = 0.01
Base* + SGA	0.75 (0.69-0.80)	t = 2.01, P = 0.05
Single tests		
Base* + cholesterol	0.74 (0.69-0.79)	t = 1.72, P = 0.09
Base* + albumin	0.75 (0.70-0.81)	t = 2.24, P = 0.03
Base* + lymphocyte	0.72 (0.67-0.78)	t = 0.63, P = 0.53

*Base model: NYHA (III/IV vs I/II), log [NT-proBNP], cardiac rhythm (AF vs SR)

AF= atrial fibrillation, SR= sinus rhythm, NYHA= New York Heart Association, NT-proBNP= N-terminal pro-B-type natriuretic peptide, BMI= body mass index, CONUT = Controlling nutritional status score, GNRI = geriatric nutritional risk index, PNI = prognostic nutritional index, MUST= malnutrition universal screening tool, MNA-SF= mini nutritional assessment –short form, SGA = subjective global assessment, CI = confidence interval.

Figure 10.1 shows the Kaplan Meier curves illustrating the relation between malnutrition and all-cause mortality. Patients who were ≥moderately malnourished according to CONUT score, MNA-SF and albumin, had a 6 to 10 times greater mortality risk than those who were not malnourished.

Figure 10.1: Kaplan Meier curves illustrating the relation between malnutrition tools and all-cause mortality (Top panel: simple tools; middle panel: multi-dimensional tools; bottom panel: laboratory tests).



The 3-month, 6-month and 12-month mortality according to malnutrition categories are shown in Tables 10.6a-c. Worsening malnutrition was associated with higher mortality rates. Patients with the worst nutritional status, had a much higher 1-year mortality rate (33-47%) than those with the best nutritional status (2-4%).

Table 10.6a: 3-month, 6-month and 12-month mortality by categories of CONUT. (Expressed as mortality rate (%), number of deaths)

	Worsening malnutrition by CONUT				P
	0-1 (N=187)	2-3 (N=190)	4-5 (N=68)	≥ 6 (N=22)	
3 month	0	1% (N=2)	6% (N=4)	9% (N=2)	<0.001
6 month	0	4% (N=8)	19% (N=13)	18% (N=4)	<0.001
12 month	2% (N=4)	13% (N=25)	28% (N=19)	36% (N=8)	<0.001

Table 10.6b: 3-month, 6-month and 12-month mortality by categories of MNA-SF. (Expressed as mortality rate (%), number of deaths)

	Worsening malnutrition by MNA-SF				P
	13-14 (N=241)	11-12 (N=132)	9-10 (N=61)	≤ 8 (N=30)	
3 month	0	0	7% (N=4)	13% (N=4)	<0.001
6 month	0 (N=1)	4% (N=5)	18% (N=11)	23% (N=7)	<0.001
12 month	4% (N=10)	11% (N=15)	32% (N=20)	33% (N=10)	<0.001

Mortality Rate: <5% 5-10% 10-20% 20-50%

Table 10.6c: 3-month, 6-month and 12-month mortality by categories of albumin. (Expressed as mortality rate (%), number of deaths)

	Worsening malnutrition by albumin				P
	≥ 40 (N=75)	35-39 (N=276)	31-34 (N=99)	≤ 30 (N=17)	
3 month	0	0 (N=1)	4% (N=4)	18% (N=3)	<0.001
6 month	3% (N=2)	2% (N=5)	13% (N=13)	29% (N=5)	<0.001
12 month	4% (N=3)	7% (N=20)	25% (N=25)	47% (N=8)	<0.001

Mortality Rate: <5% 5-10% 10-20% 20-50%

The cause of death data for CHF patients have been shown in Table 8.6.

According to the CONUT score or MNA-SF, malnourished patients suffered more cardiovascular than non-cardiovascular deaths (Table 10.7). In particular, malnourished patients suffered more deaths due to progression of HF and co-morbidities, while non-malnourished patients suffered more deaths due to infections.

According to serum albumin, malnourished patients suffered more non-cardiovascular than cardiovascular deaths (Table 10.7). In particular, malnourished patients suffered more deaths due to infections and co-morbidities, while non-malnourished patients suffered more deaths due to progression of HF.

Table 10.7: Cause of death at 1 year in malnourished vs non-malnourished patients by CONUT, MNA-SF and albumin. (Expressed as number of deaths, proportion of deaths due to a specific cause).

Cause of death	CONUT		MNA-SF		Albumin	
	M	**NM**	**M**	**NM**	**M**	**NM**
	N=279 Deaths: 52	N=188 Deaths: 4	N=137 Deaths: 37	N=330 Deaths: 19	N=116 Deaths: 33	N=351 Deaths: 23
Cardiovascular	29 (56%)	2 (50%)	21 (57%)	10 (52%)	14 (42%)	17 (74%)
MI	6 (12%)	0	2 (5%)	4 (21%)	3 (9%)	3 (13%)
HF	19 (37%)	1 (25%)	15 (41%)	5 (26%)	10 (30%)	10 (44%)
Arrhythmia	0	1 (25%)	0	1 (5%)	0	1 (4%)
CVD	4 (7%)	0	4 (11%)	0	1 (3%)	3 (13%)
Non-cardiovascular	23 (44%)	2 (50%)	16 (43%)	9 (48%)	19 (58%)	6 (26%)
Infection	13 (25%)	2 (50%)	9 (24%)	6 (33%)	10 (31%)	5 (22%)
Renal failure	1 (2%)	0	0	1 (5%)	1 (3%)	0
Co-morbidities	9 (17%)	0	7 (19%)	2 (10%)	8 (24%)	1 (4%)
Malignancy	4 (7%)	0	3 (8%)	1 (5%)	3 (9%)	1 (4%)
COPD	1 (2%)	0	0	1 (5%)	1 (3%)	0
Dementia	3 (6%)	0	3 (8%)	0	3 (9%)	0
Parkinson's	1 (2%)	0	1 (3%)	0	1 (3%)	0

MI= myocardial infarction, CVD= cerebrovascular disease, COPD= chronic obstructive pulmonary disease, CFS= Clinical frailty scale, DI= Deficit index, 5MWT= 5 meter walk test, M = malnourished, NM= non-malnourished.

10.4.3 Relation between malnutrition and combined hospitalisation and mortality

During follow up, 43% of patients were either hospitalised or died. The influence of malnutrition measures considered as univariable predictors of the combined outcome is shown in Table 10.8. Univariable analysis of clinical factors predicting the combined outcome has been shown in Table 8.8b. The presence of malnutrition, as determined by

any tool, except serum cholesterol (when used as a binary variable), was associated with an increased risk of the combined outcome.

Table 10.8: Univariable analysis of malnutrition tools predicting combined outcome.

Worse outcome per unitary increase		HR (95%CI)	χ^2	P
Laboratory tests	Albumin (g/L)	0.83 (0.80-0.87)	73.1	<0.001
	Albumin (Mal vs not mal)	2.96 (2.23-3.93)	56.5	<0.001
	Cholesterol (mmol/L)	0.85 (0.75-0.97)	6.3	0.01
	Cholesterol (Mal vs not mal)	1.20 (0.90-1.60)	1.5	0.23
	Lymphocyte ($x10^9$/L)	0.63 (0.49-0.80)	14.0	0.001
	Lymphocyte (Mal vs not mal)	1.38 (1.04-1.81)	5.1	0.02
Simple	CONUT	1.41 (1.31-1.51)	88.0	<0.001
	CONUT (Mal vs not mal)	2.20 (1.62-3.01)	24.9	<0.001
	GNRI	0.97 (0.96-0.98)	25.8	<0.001
	GNRI (Mal vs not mal)	2.57 (1.90-3.47)	37.5	<0.001
	PNI	0.89 (0.86-0.91)	62.6	<0.001
	PNI (Mal vs not mal)*	4.44 (2.94-6.69)	50.5	<0.001
Multi-dimensional	MUST	1.61 (1.37-1.90)	32.4	<0.001
	MUST (Mal vs not mal)	3.13 (2.24-4.37)	44.9	<0.001
	MNA-SF	0.76 (0.72-0.80)	94.9	<0.001
	MNA-SF (Mal vs not mal)	3.66 (2.77-4.84)	83.3	<0.001
	SGA	2.77 (2.23-3.45)	83.5	<0.001
	SGA (Mal vs not mal)	3.64 (2.73-4.85)	77.6	<0.001

Mal= malnourished, CONUT = Controlling nutritional status score, GNRI = geriatric nutritional risk index, PNI = prognostic nutritional index, MUST= malnutrition universal screening tool, MNA-SF= mini nutritional assessment –short form, SGA = subjective global assessment.

*moderate malnutrition vs no malnutrition (PNI classifies patients as non-malnourished, moderately or severely malnourished)

Clinical variables included in multivariable analyses for predicting the combined outcome are shown in Table 10.9a. All malnutrition tools, with the exception of total lymphocyte count and serum cholesterol level, were significant predictors of the combined outcome when evaluated individually in multivariable analysis (Table 10.9b).

Table 10.9a: Clinical variables included in multivariable analyses for predicting the combined outcome. (using CONUT as an example)

Worse outcome per unitary increase	**HR (95%CI)**	**χ^2**	**P**
Age (years)	1.00 (0.98-1.02)	0.02	0.90
BMI (kg/m^2)	0.99 (0.97-1.02)	0.5	0.49
NYHA (III/IV vs I/II)	1.56 (1.12-2.16)	7.0	0.008
Charlson Score	1.18 (1.10-1.27)	19.4	<0.001
Log [NT-proBNP] (ng/L)	1.38 (0.95-1.99)	2.9	0.09
Hb (g/L)	0.99 (0.98-1.00)	7.2	0.007
eGFR (mL/min per 1.73 m^2)	1.00 (0.99-1.01)	0.01	0.91
CONUT	**1.23 (1.13-1.34)**	**23.5**	**<0.001**

Cardiac rhythm (AF vs SR) is not included in multivariable analysis predicting combined outcome as it is not a significant predictor of combined outcome in univariable analysis.

HR = hazard ratio, CI= confidence interval, χ^2= chi-square, BMI= body mass index, AF= atrial fibrillation, SR= sinus rhythm, NYHA= New York Heart Association, NT-proBNP= N-terminal pro-B-type natriuretic peptide, Hb= haemoglobin, eGFR = estimated glomerular filtration rate, CONUT = Controlling nutritional status score.

Figure 10.2 shows the Kaplan Meier curves illustrating the relation between malnutrition and the combined outcome. Patients who were ≥moderately malnourished according to CONUT score, MNA-SF and albumin, had a 5 to 11 times greater risk of the combined outcome than those who were not malnourished.

The 3-month, 6-month and 12-month combined event rates according to malnutrition categories are shown in Tables 10.10a-c. Worsening malnutrition was associated with higher combined event rates. Patients with the worst nutritional status, had a much higher 3-month combined event rate (27-47%) than those with the best nutritional status (5-8%). A similar trend was seen in 6-month and 12-month combined event rates.

Table 10.9b: Multivariable analysis of malnutrition tools predicting combined outcome. (Separate multivariable analysis was performed for each tool as both a binary and a continuous variable, with Table 10.9a showing the clinical variables included in multivariable analyses for predicting the combined outcome)

Worse outcome per unitary increase		HR (95%CI)	χ^2	P
Laboratory tests	Albumin (g/L)	0.90 (0.86-0.95)	18.5	<0.001
	Albumin (Mal vs not mal)	1.96 (1.45-2.65)	18.9	<0.001
	Cholesterol (mmol/L)	0.91 (0.80-1.03)	2.1	0.15
	Cholesterol (Mal vs not mal)	1.27 (0.95-1.70)	2.5	0.11
	Lymphocyte ($x10^9$/L)	0.91 (0.73-1.14)	0.7	0.41
	Lymphocyte (Mal vs not mal)	0.94 (0.70-1.25)	0.2	0.66
Simple	CONUT	1.23 (1.13-1.34)	23.5	<0.001
	CONUT (Mal vs not mal)	1.52 (1.10-2.11)	6.3	0.01
	GNRI	0.99 (0.97-1.00)	5.9	0.02
	GNRI (Mal vs not mal)	1.84 (1.31-2.59)	12.4	<0.001
	PNI	0.95 (0.92-0.98)	10.7	0.001
	PNI (Mal vs not mal)*	2.18 (1.36-3.48)	10.6	0.001
Multi-dimensional	MUST	1.27 (1.05-1.53)	5.8	0.02
	MUST (Mal vs not mal)	2.01 (1.38-2.95)	13.0	<0.001
	MNA-SF	0.85 (0.79-0.91)	21.2	<0.001
	MNA-SF (Mal vs not mal)	2.12 (1.55-2.90)	21.9	<0.001
	SGA	1.97 (1.41-2.76)	15.9	<0.001
	SGA (Mal vs not mal)	2.37 (1.58-3.54)	17.6	<0.001

Variables in multivariable analysis predicting combined outcome included: Age, BMI, NYHA (III/IV vs I/II), Charlson score, log[NT-proBNP], Hb, eGFR (AF vs SR is not included as it is not a significant predictor of combined outcome in univariable analysis; BMI is not included in multivariable analysis involving MNA-SF, GNRI or MUST as it is part of these scores).

*moderate malnutrition vs no malnutrition (PNI classifies patients as non-malnourished, moderately or severely malnourished)

Mal= malnourished, CONUT = Controlling nutritional status score, GNRI = geriatric nutritional risk index, PNI = prognostic nutritional index, MUST= malnutrition universal screening tool, MNA-SF= mini nutritional assessment –short form, SGA = subjective global assessment.

Figure 10.2: Kaplan Meier curves illustrating the relation between malnutrition tools and combined outcome (Top panel: simple tools; middle panel: multi-dimensional tools; bottom panel: laboratory tests).

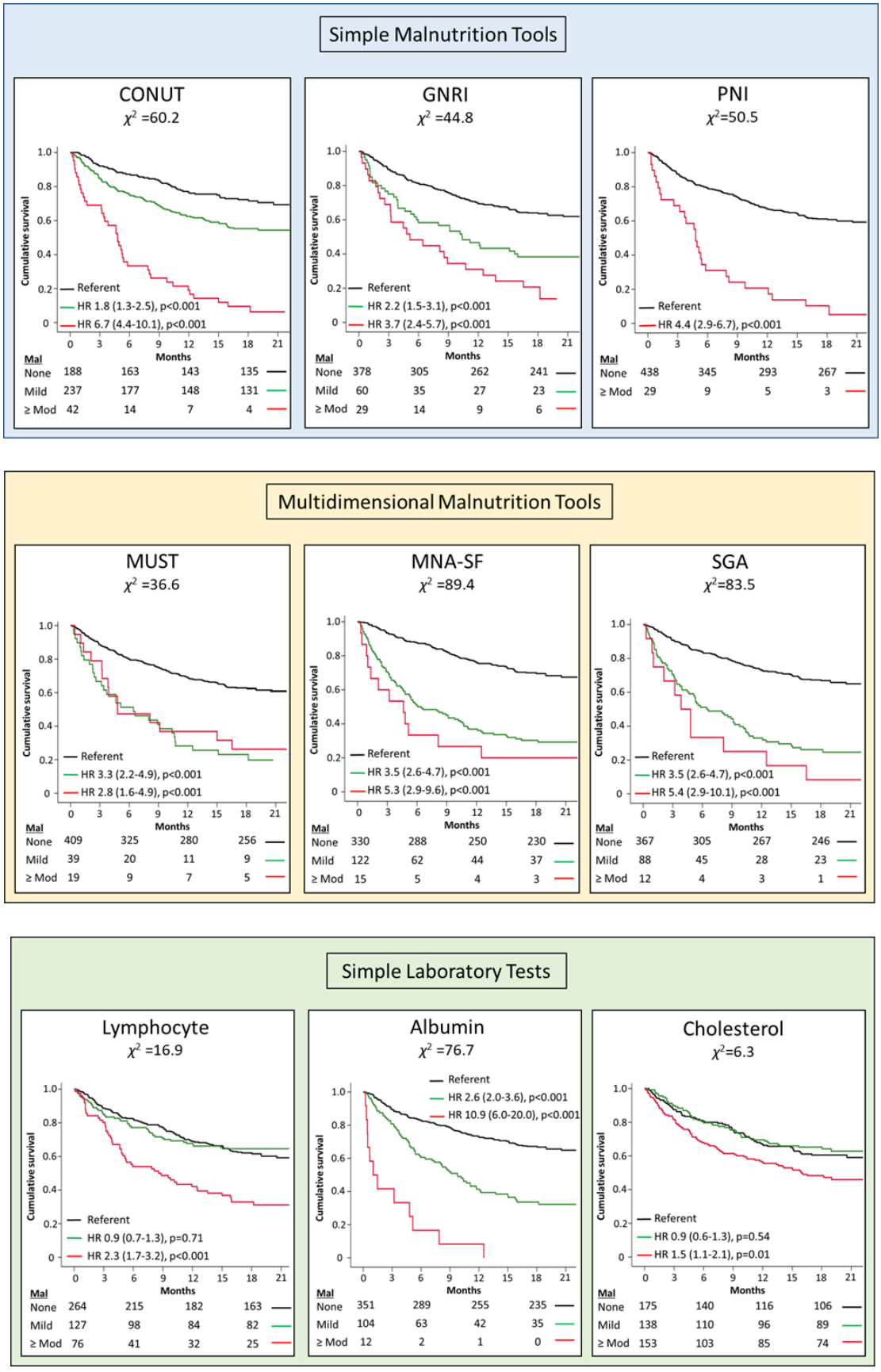


Table 10.10a: 3-month, 6-month and 12-month combined event rate by categories of CONUT.

(Expressed as combined outcome rate (%), number of events).

	Worsening malnutrition by CONUT				P
	0-1 (N=187)	2-3 (N=190)	4-5 (N=68)	≥ 6 (N=22)	
3 month	8% (N=15)	12% (N=23)	28% (N=19)	32% (N=7)	<0.001
6 month	13% (N=25)	20% (N=38)	50% (N=34)	73% (N=16)	<0.001
12 month	24% (N=45)	32% (N=60)	68% (N=46)	82% (N=18)	<0.001

Table 10.10b: 3-month, 6-month and 12-month combined event rate by categories of MNA-SF.

(Expressed as combined outcome rate (%), number of events)

	Worsening malnutrition by MNA-SF				P
	13-14 (N=241)	11-12 (N=132)	9-10 (N=61)	≤ 8 (N=30)	
3 month	5% (N=13)	15% (N=20)	38% (N=23)	27% (N=8)	<0.001
6 month	10% (N=23)	27% (N=35)	61% (N=37)	57% (N=17)	<0.001
12 month	22% (N=54)	36% (N=48)	71% (N=43)	73% (N=22)	<0.001

Event rate: <10% 10-20% 21-40% 41-70% >70%

Table 10.10c: 3-month, 6-month and 12-month combined event rate by categories of albumin. (Expressed as combined outcome rate (%), number of events)

	Worsening malnutrition by albumin				P
	≥ 40 (N=75)	35-39 (N=276)	31-34 (N=99)	≤ 30 (N=17)	
3 month	8% (N=6)	11% (N=31)	19% (N=19)	47% (N=8)	<0.001
6 month	12% (N=9)	19% (N=53)	39% (N=39)	71% (N=12)	<0.001
12 month	23% (N=17)	29% (N=79)	60% (N=59)	82% (N=14)	<0.001

Event rate: <10% 10-20% 21-40% 41-70% >70%

10.4.4 Relation between malnutrition and hospitalisation

Hospitalisation data for patients with CHF has been shown in Table 8.11. During follow up, 32% of patients had ≥1 non-elective hospitalisation within 1 year. The non-elective hospitalisation rate was significantly higher (1.8-2.6 times, depending on the tool used) in malnourished compared to non-malnourished patients (Table 10.11).

The relationship between number of hospitalisations and malnutrition categories are shown in Tables 10.12a-c. Worsening malnutrition was associated with increasing number of hospitalisations.

Table 10.11: Number of hospitalisations and length of stay within 1 year in malnourished vs non-malnourished patients by CONUT, MNA-SF and albumin.

	CONUT			MNA-SF			Albumin		
	M N=279	**NM** N=188	P	**M** N=137	**NM** N=330	P	**M** N=116	**NM** N=351	P
All admission (including same day discharge & elective admission)	131 (47%)	58 (31%)	0.001	92 (67%)	97 (29%)	*	72 (62%)	117 (33%)	*
Non-elective admission (including same day discharge)	118 (42%)	50 (27%)	0.001	85 (62%)	83 (25%)	*	68 (59%)	100 (29%)	*
Non-elective hospitalisation (excluding same day discharge)	108 (39%)	42 (22%)	*	78 (57%)	72 (22%)	*	63 (55%)	87 (24%)	*
No of hosp.			0.01			*			*
1	47 (17%)	20 (11%)		35 (26%)	32 (10%)		24 (21%)	43 (12%)	
2-3	48 (17%)	14 (7%)		30 (22%)	32 (10%)		30 (26%)	32 (9%)	
≥4	13 (5%)	8 (4%)		13 (9%)	8 (2%)		9 (8%)	12 (3%)	
Total LOS (days)	12 (5-24)	9 (3-29)	0.53	13 (5-29)	9 (4-20)	0.17	13 (5-28)	10 (4-24)	0.57
Avg LOS (days)	6 (2-10)	6 (4-12)	0.26	7 (4-12)	6 (3-10)	0.36	6 (4-13)	6 (4-10)	0.59

*P<0.001. CONUT = Controlling nutritional status score, MNA-SF= mini nutritional assessment –short form, LOS= length of stay, Avg = average, M= malnourished, NM= non-malnourished.

Table 10.12a: Number of hospitalisations within 1 year by categories of CONUT.

		Worsening malnutrition by CONUT				P
		0-1 (N=187)	2-3 (N=190)	4-5 (N=68)	≥ 6 (N=22)	
No of hospitalisations	0	73% (N=137)	69% (N=130)	41% (N=28)	18% (N=4)	<0.001
	1	15% (N=27)	16% (N=31)	25% (N=17)	14% (N=3)	<0.001
	2-3	8% (N=15)	12% (N=23)	22% (N=15)	36% (N=8)	<0.001
	≥4	4% (N=8)	3% (N=6)	12% (N=8)	32% (N=7)	<0.001

Table 10.12b: Number of hospitalisations within 1 year by categories of MNA-SF.

		Worsening malnutrition by MNA-SF				P
		13-14 (N=241)	11-12 (N=132)	9-10 (N=61)	≤ 8 (N=30)	
No of hospitalisations	0	76% (N=182)	65% (N=86)	33% (N=20)	33% (N=10)	<0.001
	1	13% (N=31)	17% (N=23)	26% (N=16)	23% (N=7)	<0.001
	2-3	9% (N=21)	14% (N=18)	21% (N=13)	36% (N=8)	<0.001
	≥4	3% (N=7)	4% (N=5)	20% (N=12)	17% (N=5)	<0.001

Table 10.12c: Number of hospitalisations within 1 year by categories of albumin.

		Worsening malnutrition by albumin				P
		≥ 40 (N=75)	35-39 (N=276)	31-34 (N=99)	≤ 30 (N=17)	
No of hospitalisations	0	76% (N=57)	70% (N=194)	46% (N=45)	18% (N=3)	<0.001
	1	14% (N=10)	15% (N=42)	23% (N=23)	18% (N=3)	<0.001
	2-3	9% (N=7)	9% (N=25)	22% (N=22)	41% (N=7)	<0.001
	≥4	1% (N=1)	6% (N=15)	9% (N=9)	23% (N=4)	<0.001

The cause of hospitalisation data for CHF patients have been shown in Table 8.14. Malnourished patients suffered more non-cardiovascular than cardiovascular hospitalisations (Table 10.13). Of non-cardiovascular hospitalisations, malnourished patients suffered more hospitalisations due to infections and acute kidney injury (AKI) while non-malnourished patients suffered more hospitalisations due to co-morbidities. HF hospitalisation rate was similar in malnourished compared to non-malnourished patients.

Table 10.13: Cause of hospitalisation within 1 year in malnourished vs non-malnourished patients by CONUT, MNA-SF and albumin. (Expressed as number of hospitalisations, proportion of hospitalisations due to a specific cause)

Cause of Hospitalisation	CONUT		MNA-SF		Albumin	
	M	**NM**	**M**	**NM**	**M**	**NM**
	N=279 Hosp = 228	N=188 Hosp = 94	N=137 Hosp = 177	N=330 Hosp = 150	N=116 Hosp = 140	N=351 Hosp = 182
Cardiovascular	83 (37%)	41 (44%)	68 (38%)	59 (39%)	44 (31%)	80 (44%)
HF	58 (25%)	25 (27%)	50 (28%)	36 (24%)	33 (23%)	50 (28%)
ACS	6 (3%)	4 (4%)	2 (1%)	8 (6%)	4 (3%)	6 (3%)
Angina	4 (2%)	1 (1%)	3 (2%)	2 (1%)	1 (1%)	4 (2%)
Arrhythmia	4 (2%)	5 (6%)	6 (3%)	3 (2%)	1 (1%)	8 (5%)
CVD	6 (3%)	2 (2%)	3 (2%)	5 (3%)	2 (1%)	6 (3%)
PVD	5 (2%)	4 (4%)	4 (2%)	5 (3%)	3 (2%)	6 (3%)
Non-cardiovascular	145 (64%)	53 (56%)	109 (62%)	91 (61%)	96 (69%)	102 (56%)
Infection	53 (23%)	14 (15%)	39 (22%)	27 (18%)	38 (27%)	29 (16%)
Falls	37 (16%)	15 (16%)	28 (16%)	27 (18%)	22 (18%)	30 (16%)
AKI	18 (8%)	4 (4%)	13 (7%)	9 (6%)	12 (8%)	10 (5%)
Bleeding	5 (2%)	1 (1%)	3 (2%)	3 (2%)	4 (3%)	2 (1%)
Co-morbidities	26 (12%)	16 (17%)	20 (12%)	22 (15%)	16 (10%)	26 (15%)
COPD	11 (5%)	9 (10%)	11 (7%)	11 (6%)	6 (4%)	14 (8%)
Malignancy	4 (2%)	2 (2%)	2 (1%)	4 (3%)	2 (1%)	4 (2%)
Anaemia	3 (1%)	1 (1%)	1 (1%)	3 (2%)	2 (1%)	2 (1%)
General decline	2 (1%)	1 (1%)	2 (1%)	1 (1%)	2 (1%)	1 (1%)
Other	6 (3%)	3 (3%)	4 (2%)	3 (3%)	4 (3%)	5 (3%)
Medication-related	6 (3%)	3 (3%)	6 (3%)	3 (2%)	4 (3%)	5 (3%)

ACS = acute coronary syndrome, CVD= cerebrovascular disease, PVD= peripheral vascular disease, AKI= acute kidney injury, COPD= chronic obstructive pulmonary disease, CONUT = Controlling nutritional status score, MNA-SF= mini nutritional assessment –short form.

10.4.5 Malnutrition and body composition

For a subset of patients (N=233), body composition measurements were available. 72 patients were unable to have body composition measurements due to poor mobility; 107 patients had either a pacemaker or a defibrillator; 55 patients refused further testing. Body composition data of CHF patients are presented in Table 10.14a.

Table 10.14a: Body composition of CHF patients.

	CHF (N=233)
Weight (kg)	84 (72-100)
BMI (kg/m^2)	30 (26-34)
Fat mass (%)	30 (23-36)
Total body water (kg)	41 (36-47)
ECW (kg)	18 (16-21)
ICW (kg)	23 (20-27)
ECW/ICW	0.81 (0.75-0.88)
Body water (%)	49 (45-53)
Muscle mass (%)	66 (60-73)
Impedence (Ω)	458 (357-527)

CONUT = Controlling nutritional status score, MNA-SF= mini nutritional assessment –short form, mal= malnourished, BMI= body mass index, ECW= extracellular water, ICW= intracellular water

The body composition of malnourished compared to non-malnourished patients varied according to the malnutrition tool used (Table 10.14b). Generally, the fat mass percentage and impedance were lower but muscle mass percentage was higher in malnourished compared to non-malnourished patients.

Table 10.14b: Body composition in malnourished vs non-malnourished patients by CONUT, MNA-SF and albumin.

	CONUT			MNA-SF			Albumin		
	M N=124	**NM** N=109	P	**M** N=51	**NM** N=182	P	**M** N=51	**NM** N=182	P
Weight (kg)	80 (71-100)	90 (75-102)	0.10	75 (61-93)	88 (74-102)	*	80 (72-97)	86 (71-102)	0.34
BMI (kg/m^2)	29 (26-33)	30 (26-35)	0.12	26 (22-32)	30 (27-35)	*	29 (26-33)	30 (26-35)	0.51
Fat mass (%)	29 (21-34)	33 (25-39)	*	27 (15-34)	30 (25-37)	0.01	29 (22-34)	30 (24-37)	0.11
Total body water (kg)	41 (37-47)	42 (35-47)	0.79	39 (30-46)	42 (37-48)	0.01	42 (37-47)	41 (35-47)	0.57
ECW (kg)	19 (16-20)	18 (16-21)	0.90	17 (14-19)	19 (17-21)	0.002	19 (16-20)	18 (16-21)	0.99
ICW (kg)	23 (20-28)	23 (19-27)	0.53	21 (16-26)	24 (20-28)	0.02	24 (21-27)	23 (19-28)	0.45
ECW/ICW	0.81 (0.74-0.86)	0.81 (0.75-0.90)	0.25	0.82 (0.72-0.93)	0.80 (0.75-0.87)	0.38	0.80 (0.71-0.87)	0.81 (0.75-0.88)	0.49
Body water (%)	49 (46-55)	47 (43-51)	*	50 (46-58)	48 (45-52)	0.01	49 (45-55)	48 (45-52)	0.12
Muscle mass (%)	67 (63-75)	64 (58-71)	0.002	68 (62-81)	66 (60-71)	0.02	67 (62-74)	66 (60-72)	0.15
Impedence (Ω)	422 (329-510)	487 (414-553)	*	384 (273-528)	463 (383-526)	0.09	399 (273-518)	465 (380-528)	0.02

*P<0.001.

CONUT = Controlling nutritional status score, MNA-SF= mini nutritional assessment –short form, mal= malnourished, BMI= body mass index, ECW= extracellular water, ICW= intracellular water.

10.5 Discussion

This study is the first to make a comprehensive comparison of the prognostic value of several commonly used malnutrition tools in a well-characterised cohort of ambulatory patients with CHF. The main finding is that malnutrition was a powerful predictor of morbidity and mortality, regardless of the tool used, and independent of age, co-morbidities, HF symptoms and severity. Results from this study confirm, and expand on previous findings from other HF cohorts, which demonstrated malnutrition as a predictor of worse outcome (157).

Many novel malnutrition tools incorporating different combinations of clinical and biochemical factors have been developed and are strong predictors of adverse outcomes (118). However, the impact of individual factors on the overall prognostic performance of combination tools is unclear. Up to 25% of ambulatory patients with CHF have hypoalbuminemia, and the proportion is greater amongst those requiring recurrent hospitalisations. This study showed that serum albumin has a similar prognostic value as the more complex malnutrition tools, and it is clearly very simple to determine.

Disadvantages to using albumin in isolation as a diagnostic tool for malnutrition include the fact that albumin levels can be affected by acute illness, inflammation, liver dysfunction and/or haemodilution, raising doubts about its reliability as a marker for malnutrition. Secondly, albumin has a long half-life (14-20 days) and does not identify acute changes in nutritional status (193).

Simple malnutrition tools such as CONUT score, GNRI and PNI, measure malnutrition using a combination of laboratory tests and anthropometric measures in addition to albumin. They can generally be completed within a minute. CONUT score uses serum albumin, cholesterol and lymphocyte count. Its use in patients with CHF is potentially limited by statin use. PNI only classifies patients as either non-malnourished or ≥moderately malnourished, and therefore underestimates the prevalence of milder degrees of malnutrition. GNRI takes into account weight, which might be confounded by fluid status, and underestimate malnutrition in obese patients as discussed in Chapter 6.

Multi-dimensional tools, such as MUST, MNA-SF and SGA, offer a more comprehensive approach to assess nutritional status by taking into account a variety of clinical and dietary

factors, but have subjective components and are time-consuming to perform (20 minutes for SGA). A recent systematic review which included 28 observational studies on malnutrition tools and clinical outcomes in patients with AHF or CHF, concluded that amongst 11 malnutrition tools, MNA has the best predictive ability for mortality (118). However, the reliability of these results is limited as they were generated from a meta-analysis of observational studies investigating different malnutrition tools. The only reliable way to compare the prognostic value of different malnutrition tools is to evaluate them simultaneously in the same cohort of patients, as demonstrated in this study.

The pathophysiology of malnutrition in patients with HF is not well understood. Several theories have been proposed to explain the complex relationship between malnutrition and HF, however, no causality has been established yet. One possibility is that fluid retention might cause gut oedema leading to nausea, anorexia and possibly malabsorption (194). A second possibility is that change in gut morphology and function disrupts the immunological barrier of the bowel wall, triggering release of pro-inflammatory cytokines. Chronic inflammation and neurohormonal activation in HF also promote catabolism, leading to protein and fat tissue degradation, and thus weight loss and cachexia (195, 196).

Malnutrition predisposes to cachexia which is associated with functional impairment, reduced QoL, increased morbidity and mortality (91). Early identification of malnutrition in patients with CHF may allow initiation of potential treatment to prevent the development of cachexia. Firstly, optimisation of HF therapy might help stabilise systemic haemodynamics and improve bowel oedema (197). Secondly, regular nutritional counselling and promotion of a high caloric and high protein diet might help ensure adequate dietary intake (197). Micronutrient and vitamin supplementation might also be helpful (159, 197). Regular physical exercise has anti-inflammatory effect and might ameliorate progressive tissue wasting (197). Other mechanistically appealing treatments include appetite stimulants, anti-inflammatory agents and anabolic hormones, but their role in the treatment of malnutrition is unclear (91).

10.6 Study limitations

This is a single-centre study with limited sample size. Therefore, external validation of our results from other populations is needed. This study is, however, the most comprehensive study which directly compares the prognostic value of several commonly used malnutrition tools as well as laboratory tests in consecutive, unselected, ambulatory patients with CHF. However, I have only studied 9 of the most commonly used malnutrition tools. There are other tools which identified patients at increased risk of adverse outcomes in other clinical scenarios (118).

This study has limited follow up. Therefore, I am unable to comment on long-term prognostic significance of malnutrition in CHF patients. However, the majority of patients identified as malnourished have had an end-point by the end of the study. I also did not investigate the relationship between malnutrition tools, body composition and outcome; or study the change in nutritional status over time.

10.7 Conclusion

Malnutrition is a strong predictor of morbidity and mortality in ambulatory patients with CHF. Malnutrition evaluation should therefore be routinely performed in clinical practice to identify patients at high risk. Measuring serum albumin provides comparable prognostic information to simple or multi-dimensional tools, therefore might be a good initial tool to screen for malnutrition in patients with CHF.

Chapter 11 Malnutrition, Congestion and Mortality in Patients with Chronic Heart Failure

11.1 Chapter summary

Background: In patients with CHF, malnutrition might be related to right heart dysfunction and venous congestion, which predispose to bowel oedema and malabsorption, thereby leading to malnutrition.

Aims: To study the relation between malnutrition, congestion and mortality in a large cohort of ambulatory patients with CHF.

Methods: I evaluated malnutrition using Geriatric nutritional risk index (GNRI). Congestion was defined by echocardiography (raised right atrial pressure (RAP) = dilated inferior vena cava (IVC) ≥21 mm/ raised pulmonary artery systolic pressure (PAsP) = trans-tricuspid gradient ≥36mmHg/ right ventricular systolic dysfunction (RVSD) = tricuspid annular plane systolic excursion (TAPSE) <17mm).

Results: I enrolled 1054 patients; CHF was confirmed in 952 (69% males, median age 75 (IQR: 67-81) years, median NT-proBNP 1141 (IQR: 465-2562) ng/L). 39% had HeFREF (LVEF<40%) and 61% had HeFNEF (LVEF≥40%, NT-proBNP >125 ng/L).

Overall, 14% of CHF patients were malnourished (GNRI ≤98). 35% had raised RAP, 23% had raised PAsP and 38% had RVSD. Malnutrition and congestion are modestly correlated.

During a median follow-up of 1683 (IQR: 1096-2230) days, 461 (44%) patients died. Malnutrition was an independent predictor of mortality. Patients who were malnourished with both RVSD and increased RAP had a 6-fold increased risk of mortality compared to non-malnourished patients without RVSD who had normal RAP.

Conclusion: In patients with CHF, malnutrition and congestion are modestly correlated and each is independently associated with increased mortality. CHF patients with both malnutrition and congestion as evidenced by right heart dysfunction should be managed with additional vigilance.

11.2 Introduction

Frailty and malnutrition predispose to the development of cachexia in patients with HF and are associated with worse prognosis (91, 118). However, the underlying pathophysiological mechanism is not fully understood. In previous chapters, I have explored in depth the prevalence and prognostic significance of frailty and malnutrition in different populations of patients with HF. In the following two chapters, I will explore possible underlying mechanisms of these conditions.

CHF is characterised by congestion and high systemic venous pressures. Previous work has suggested that cachexia and malnutrition in CHF are associated with high right atrial pressure (RAP) and tricuspid regurgitation (129, 198). Right ventricular (RV) dysfunction has also been shown to be associated with intestinal and liver congestion and abnormal body composition in cachectic patients with CHF (92, 199, 200). However, the relation between malnutrition, RV dysfunction and systemic venous congestion in patients with CHF has not been studied.

I hypothesize that patients with CHF who have significant clinical congestion, high RAP and RV dysfunction might be at risk of developing congestive enteropathy, malabsorption and anorexia, thereby leading to clinical malnutrition and worse outcome. In this chapter, I will study the relation between malnutrition and congestion (assessed clinically and with echocardiography), and their relation to outcome in a large cohort of well-characterised ambulatory patients with CHF.

11.3 Methods

11.3.1 Study population

I enrolled a subset of patients from the Hull Lifelab who attended our community HF clinic between 2008-2012, for whom detailed echocardiographic images were available. All patients had a full medical history, a physical examination and blood tests during baseline visit. CHF patients were phenotyped as HeFREF or HeFNEF according to the

HF definitions detailed in Chapter 4. A detailed description of the study population and relevant examinations can be found in Chapter 4.

11.3.2 Congestion score

A congestion score was constructed, based on the following examination findings:

- Lung auscultation (normal, basal, mid-zone or diffuse crackles)
- JVP (not visible, raised 1-4 cm, raised to earlobe)
- Peripheral oedema (none, ankles, below/above knees)
- Liver examination (not palpable, palpable)

1 point was attributed for each degree of severity of abnormal examination findings. The total possible score was 9. Patients with a score of ≥3 were defined as severely congested (201).

11.3.3 Echocardiographic definitions

LV systolic function was measured by calculating LVEF using Simpson's method. Left atrial (LA) dilatation was measured by left atrial volume index (LAVI). Patients with LAVI >34 mL/m^2 were considered to have LA dilatation (202). RV systolic function was measured by TAPSE. Patients with TAPSE <17mm were considered to have RVSD (202). RV systolic pressure and RAP were estimated from the maximal tricuspid regurgitation velocity (TR Vmax) and inferior vena cava (IVC) diameter respectively. Patients with trans-tricuspid gradient ≥36mmHg were considered to have raised PAsP (202). Patients with IVC diameter ≥21 mm were considered to have an increased RAP (202). Mitral and tricuspid regurgitation were assessed semi-quantitatively and expressed in 4 grades (absent, mild, moderate or severe).

11.3.4 Malnutrition evaluation

In Chapter 6, I have evaluated malnutrition using 3 simple malnutrition tools in patients with CHF and found that Geriatric nutritional risk index (GNRI) has better prognostic value compared to COntroling NUTritional Status (CONUT) score and Prognostic nutritional index (PNI). Therefore, in this chapter, I evaluated malnutrition using GNRI. A description of the malnutrition evaluation process for GNRI can be found in the 'malnutrition evaluation' section in Chapter 4.

11.3.5 End point and follow up

I followed the patients until 1st May 2016 and the primary endpoint was all-cause mortality.

11.3.6 Statistical analysis

Routine statistical analyses have been detailed in Chapter 4.

Firstly, I studied the association between malnutrition and congestion (clinical and echocardiographic) using logistic regression analysis. Then, I studied the impact of congestion and malnutrition on survival using Cox proportional hazard regression. Finally, I created a base model for predicting mortality using the following variables: age, systolic BP, NYHA class, urea and log [NT-proBNP]. I then added the malnutrition score (GNRI), markers of congestion (clinical and echocardiographic) and combinations of malnutrition and markers of congestion in turn to the base model and used Harrell's C-statistic and net reclassification index (NRI) to evaluate model discrimination.

11.4 Results

11.4.1 Baseline characteristics

Baseline characteristics (clinical data and measures of congestion) of patients with CHF vs those without HF are shown in Tables 11.1a-b. Of the 1054 patients enrolled, CHF was confirmed in 952. 69% of patients with CHF were male and 39% had HeFREF. The median age was 75 years and median NT-proBNP was 1141 ng/L. 10% had mild malnutrition and 4% had moderate to severe malnutrition (Table 11.1a).

Table 11.1a: Baseline characteristics of patients with CHF vs those without HF.

	No HF N=102	**CHF** N=952	Missing	**P**
Demographics				
Age (years)	64 (50-70)	75 (67-81)	0	<0.001
Sex (male), n (%)	71 (70)	655 (69)	0	0.87
BP systolic (mmHg)	133 (118-151)	126 (111-144)	0	0.01
HR (bpm)	71 (63-80)	70 (61-78)	0	0.27
Height (m)	1.70 (1.61-1.77)	1.69 (1.61-1.75)	0	0.26
Weight (kg)	88 (76-100)	80 (68-95)	0	0.002
BMI (kg/m^2)	30 (27-34)	28 (25-32)	0	0.002
NYHA III/IV, n (%)	11 (11)	317 (33)	0	<0.001
SR, n (%)	102 (100)	606 (64)	0	<0.001
Co-morbidities				
IHD, n (%)	33 (32)	579 (61)	0	<0.001
HTN, n (%)	57 (56)	498 (52)	0	0.49
CVD, n (%)	5 (5)	90 (10)	0	0.13
Diabetes Mellitus, n (%)	28 (28)	285 (30)	0	0.60
COPD, n (%)	11 (11)	109 (11)	0	0.84
Dyslipidaemia, n (%)	35 (34)	199 (21)	0	0.002

Table 11.1a (continued): Baseline characteristics of patients with CHF vs those without HF.

	No HF N=102	**CHF** N=952	Missing	**P**
Medications				
ACEi/ARB, n (%)	67 (66)	805 (85)	0	<0.001
BB, n (%)	44 (43)	736 (77)	0	<0.001
MRA, n (%)	21 (21)	344 (36)	0	0.002
Loop diuretics, n (%)	36 (35)	661 (69)	0	<0.001
Digoxin, n (%)	5 (5)	210 (22)	0	<0.001
Statin, n (%)	56 (55)	636 (67)	0	0.02
Blood tests				
NT-proBNP (ng/L)	59 (33-93)	1141 (465-2562)	1	<0.001
Hb (g/dL)	14.1 (13.2-15.4)	13.3 (12.0-14.3)	0	<0.001
Sodium (mmol/L)	139 (138-140)	138 (136-140)	1	0.12
Potassium (mmol/L)	4.3 (4.0-4.5)	4.4 (4.1-4.7)	0	0.002
Urea (mmol/L)	4.9 (3.9-6.1)	7.3 (5.5-10.2)	0	<0.001
Creatinine (umol/L)	84 (70-98)	103 (84-134)	0	<0.001
Albumin (g/L)	41 (38-42)	38 (36-40)	0	<0.001
Malnutrition (GNRI)				
Normal (>98)	97 (95)	820 (86)	0	0.07
Mild (92-98)	5 (5)	98 (10)		
Moderate (82-91)	0	30 (3)		
Severe (<82)	0	4 (1)		

BMI= body mass index, BP= blood pressure, HR= heart rate, NYHA = New York Heart Association, SR= sinus rhythm, IHD = ischaemic heart disease, CVD = cerebrovascular disease, COPD= chronic obstructive pulmonary disease, Hb = Haemoglobin, NT-proBNP = N-terminal Pro Brain Natriuretic Peptide, MRA = Mineralocorticoid receptor antagonists, ACEi = Angiotensin-converting enzyme inhibitor, ARB = Angiotensin receptor blocker, BB= betablocker, GNRI = Geriatric nutritional risk index.

Table 11.1b: Echocardiographic and clinical measures of congestion in patients with CHF vs those without HF.

	No HF N=102	**CHF** N=952	Missing	**P**
Echocardiographic measures of congestion				
LVEF (%)	57 (52-63)	44 (34-55)	0	NA
LVEDD (mm)	49 (44-53)	57 (50-63)	0	<0.001
LVEDV (mL)	101 (83-123)	140 (101-189)	0	<0.001
LVESV (mL)	43 (32-58)	77 (43-120)	0	<0.001
LA diameter (mm)	38 (32-41)	43 (39-48)	0	<0.001
LA volume (mL)	47 (37-59)	80 (58-106)	0	<0.001
LAVI (mL/m^2)	23.8 (19.6-29.4)	42.2 (30.1-55.6)	0	<0.001
Mitral regurgitation (≥moderate), n (%)	0	145 (15)	1	<0.001
Tricuspid regurgitation (≥moderate), n (%)	0	85 (9)	0	<0.001
TAPSE (mm)	23 (20-25)	18 (15-21)	0	<0.001
RVSD (TAPSE <17mm), n (%)	3 (3)	360 (38)	0	<0.001
Trans-tricuspid gradient (mmHg)	17 (16-21)	25 (20-33)	38	<0.001
TR Vmax (m/s)	2.1 (2.0-2.3)	2.5 (2.2-2.9)	38	<0.001
Increased PAsP (Trans-tricuspid gradient ≥36mmHg), n (%)	0	208 (23)	38	<0.001
IVC diameter (mm)	15 (14-17)	18 (16-22)	36	<0.001
Increased RAP (IVC ≥21 mm), n (%)	2 (2)	318 (35)	36	<0.001
GLS (%)	-18 (-16 to-13)	-10 (-14 to -7)	431	<0.001
E/e’	8.0 (6.0-9.8)	11.0 (9.0-15.0)	679	<0.001

Table 11.1b (continued): Echocardiographic and clinical measures of congestion in patients with CHF vs those without HF.

	No HF N=102	**CHF** N=952	Missing	**P**
Clinical measures of congestion				
Lung crackles, n (%)	8 (8)	120 (13)	0	0.16
Palpable Liver, n (%)	0	51 (5)	0	0.02
Raised JVP (1-4cm/ to earlobe), n (%)	3 (3)	125 (13)	0	0.003
Oedema ≤ ankles, n (%)	4 (4)	154 (16)	0	0.003
Oedema > ankles, n (%)	4 (4)	48 (5)	0	0.003
Congestion score ≥3, n (%)	6 (6)	141 (15)	0	0.01

LVEF= left ventricular ejection fraction, LVEDD= left ventricular end diastolic diameter, LVEDV = left ventricular end diastolic volume, LVESV = left ventricular end systolic volume, TAPSE= tricuspid annular plane systolic excursion, RVSD= right ventricular systolic dysfunction, LA= Left atrial, LAVI= left atrial volume index, TR Vmax= maximal tricuspid regurgitation velocity, PAsP= pulmonary artery systolic pressure, RAP= right atrial pressure, IVC= inferior vena cava, GLS= left ventricular global longitudinal strain, E/e' = ratio between early mitral inflow velocity and mitral annular early diastolic velocity, JVP= jugular venous pressure.

Baseline characteristics (clinical data and measures of congestion) of patients with HeFREF vs those with HeFNEF are shown in Tables 11.2a-b. Malnutrition was more common in patients with HeFREF than HeFNEF (17% vs 12%, P=0.01) (Table 11.2a).

Table 11.2a: Baseline characteristics of HeFREF vs HeFNEF patients.

	HeFREF N=369	**HeFNEF** N=583	**P**
Demographics			
Age (years)	73 (64-79)	76 (69-82)	<0.001
Sex (male), n (%)	279 (76)	376 (65)	<0.001
BP systolic (mmHg)	120 (105-137)	131 (117-151)	<0.001
HR (bpm)	70 (62-78)	69 (60-79)	0.17
Height (m)	1.71 (1.64-1.77)	1.67 (1.59-1.74)	<0.001
Weight (kg)	79 (68-91)	80 (69-98)	0.02
BMI (kg/m^2)	27 (24-30)	29 (25-34)	<0.001
NYHA III/IV, n (%)	137 (37)	180 (31)	0.05
SR, n (%)	273 (74)	333 (57)	<0.001

Table 11.2a (continued): Baseline characteristics of HeFREF vs HeFNEF patients.

	HeFREF N=369	**HeFNEF** N=583	**P**
Co-morbidities			
IHD, n (%)	264 (72)	315 (54)	<0.001
HTN, n (%)	151 (41)	347 (60)	<0.001
CVD, n (%)	28 (8)	62 (11)	0.12
Diabetes Mellitus, n (%)	98 (27)	187 (32)	0.07
COPD, n (%)	41 (11)	68 (12)	0.79
Dyslipidaemia, n (%)	78 (21)	121 (21)	0.89
Medications			
ACEi/ARB, n (%)	337 (91)	468 (80)	<0.001
BB, n (%)	312 (85)	424 (73)	<0.001
MRA, n (%)	191 (52)	153 (26)	<0.001
Loop diuretics, n (%)	276 (75)	385 (66)	0.004
Digoxin, n (%)	78 (21)	132 (23)	0.59
Statin, n (%)	264 (72)	372 (64)	0.01
Blood tests			
NT-proBNP (ng/L)	1747 (755-3516)	880 (364-1911)	<0.001
Hb (g/dL)	13.4 (12.3-14.3)	13.1 (11.9-14.3)	0.08
Sodium (mmol/L)	138 (136-140)	138 (136-140)	0.60
Potassium (mmol/L)	4.4 (4.1-4.7)	4.4 (4.1-4.6)	0.24
Urea (mmol/L)	7.3 (5.8-10.1)	7.3 (5.4-10.4)	0.78
Creatinine (umol/L)	106 (85-137)	102 (83-133)	0.49
Albumin (g/L)	38 (36-40)	38 (36-40)	0.62
Malnutrition (GNRI)			
Normal (>98)	308 (83)	512 (88)	0.01
Mild (92-98)	51 (14)	47 (8)	
Moderate (82-91)	10 (3)	20 (3)	
Severe (<82)	0	4 (1)	

BMI= body mass index, BP= blood pressure, HR= heart rate, NYHA = New York Heart Association, SR = sinus rhythm, IHD = ischaemic heart disease, CVD = cerebrovascular disease, COPD= chronic obstructive pulmonary disease, Hb = Haemoglobin, NT-proBNP = N-terminal Pro Brain Natriuretic Peptide, MRA = Mineralocorticoid receptor antagonists, ACEi = Angiotensin-converting enzyme inhibitor, ARB = Angiotensin receptor blocker, BB= betablocker, GNRI = Geriatric nutritional risk index.

Table 11.2b: Echocardiographic and clinical measures of congestion in HeFREF vs HeFNEF patients.

	HeFREF N=369	**HeFNEF** N=583	**P**
Echocardiographic measures of congestion			
LVEF (%)	32 (26-36)	53 (46-60)	NA
LVEDD (mm)	64 (59-70)	52 (47-58)	<0.001
LVEDV (mL)	194 (156-240)	111 (84-147)	<0.001
LVESV (mL)	130 (101-170)	51 (35-74)	<0.001
LA diameter (mm)	44 (40-49)	42 (39-47)	0.001
LA volume (mL)	84 (64-112)	77 (55-103)	0.003
LAVI (mL/m^2)	45.4 (33.1-58.6)	40.2 (28.2-53.8)	0.005
Mitral regurgitation (≥moderate), n (%)	71 (20)	74 (13)	<0.001
Tricuspid regurgitation (≥moderate), n (%)	28 (7)	57 (10)	0.07
TAPSE (mm)	17 (14-20)	19 (16-22)	<0.001
RVSD (TAPSE <17mm), n (%)	184 (50)	176 (30)	<0.001
Trans-tricuspid gradient (mmHg)	26 (20-36)	25 (20-33)	0.32
TR Vmax (m/s)	2.5 (2.2-3.0)	2.5 (2.2-2.9)	0.26
Increased PAsP (Trans-tricuspid gradient ≥36mmHg), n (%)	92 (26)	116 (21)	0.07
IVC diameter (mm)	19 (16-23)	18 (16-22)	0.001
Increased RAP (IVC ≥21 mm), n (%)	142 (39)	176 (32)	0.015
GLS (%)	-8 (-7 to -5)	-13 (-16 to -10)	<0.001
E/e’	13.0 (10.0-19.5)	10.0 (8.0-14.0)	<0.001

Table 11.2b (continued): Echocardiographic and clinical measures of congestion in HeFREF vs HeFNEF patients.

	HeFREF N=369	HeFNEF N=583	P
Clinical measures of congestion			
Lung crackles, n (%)	43 (12)	77 (13)	0.48
Palpable Liver, n (%)	18 (5)	33 (6)	0.60
Raised JVP (1-4cm/ to earlobe), n (%)	52 (14)	73 (13)	0.48
Oedema ≤ ankles, n (%)	51 (14)	103 (18)	0.09
Oedema > ankles, n (%)	14 (4)	34 (6)	0.09
Congestion score ≥3, n (%)	51 (14)	90 (15)	0.49

LVEF= left ventricular ejection fraction, LVEDD= left ventricular end diastolic diameter, LVEDV = left ventricular end diastolic volume, LVESV = left ventricular end systolic volume, TAPSE= tricuspid annular plane systolic excursion, RVSD= right ventricular systolic dysfunction, LA= Left atrial, LAVI= left atrial volume index, TR Vmax= maximal tricuspid regurgitation velocity, PAsP= pulmonary artery systolic pressure, RAP= right atrial pressure, IVC= inferior vena cava, GLS= left ventricular global longitudinal strain, E/e' = ratio between early mitral inflow velocity and mitral annular early diastolic velocity, JVP= jugular venous pressure.

11.4.2 Prevalence of clinical signs of congestion

Although a small proportion of patients without HF had signs of congestion on clinical examination, patients with CHF were much more likely to have these signs (Table 11.1b). Patients with HeFREF were as likely to have clinical signs of congestion as patients with HeFNEF (Table 11.2b). Baseline characteristics by clinical congestion is shown in table 11.3.

Table 11.3: Baseline characteristics of CHF patients by clinical congestion groups.

	Clinical congestion (Congestion score ≥3)		Missing	**P**
	Yes N=141	**No** N=811		
Demographics				
Age (years)	79 (74-84)	74 (66-80)	0	<0.001
Sex (male), n (%)	96 (68)	559 (69)	0	0.84
BP systolic (mmHg)	124 (108-142)	127 (111-144)	0	0.15
HR (bpm)	72 (63-86)	70 (60-78)	0	<0.001
Weight (kg)	77 (67-95)	80 (69-95)	0	0.51
BMI (kg/m^2)	28 (25-32)	28 (25-33)	0	0.66
NYHA III/IV, n (%)	95 (67)	222 (27)	0	<0.001
SR, n (%)	63 (45)	543 (67)	0	<0.001
Co-morbidities				
IHD, n (%)	83 (59)	496 (61)	0	0.61
HTN, n (%)	72 (51)	426 (53)	0	0.75
CVD, n (%)	74 (9)	16 (11)	0	0.41
Diabetes Mellitus, n (%)	45 (32)	240 (30)	0	0.58
COPD, n (%)	16 (11)	93 (12)	0	0.97
Medications				
ACEi/ARB, n (%)	109 (77)	696 (86)	0	0.01
BB, n (%)	104 (74)	632 (78)	0	0.28
MRA, n (%)	58 (41)	286 (35)	0	0.18
Loop diuretics, n (%)	125 (89)	536 (66)	0	<0.001
Blood tests				
NT-proBNP (ng/L)	2810 (1357-4787)	1014 (409-2064)	1	<0.001
Hb (g/dL)	12.4 (11.1-13.8)	13.3 (12.2-14.4)	0	<0.001
Sodium (mmol/L)	138 (135-140)	138 (137-140)	1	0.19
Urea (mmol/L)	9.7 (6.8-13.2)	7.1 (5.4-9.8)	0	<0.001
Creatinine (umol/L)	118 (91-152)	101 (83-131)	0	0.05
Albumin (g/L)	36 (34-39)	38 (37-40)	0	<0.001

Table 11.3 (continued): Baseline characteristics of CHF patients by clinical congestion groups.

	Clinical congestion (Congestion score ≥3)		Missing	P
	Yes N=141	**No** N=811		
Malnutrition (GNRI)				
Normal (>98)	105 (75)	715 (88)	0	<0.001
Mild (92-98)	24 (17)	74 (9)		
Moderate (82-91)	10 (7)	20 (3)		
Severe (<82)	2 (2)	2 (0)		
Echocardiography				
Increased RAP (IVC ≥ 21 mm), n (%)	93 (67)	225 (29)	33	<0.001
RVSD (TAPSE <17mm), n (%)	81 (57)	279 (34)	0	<0.001
Increased PAsP (Trans-tricuspid gradient ≥36mmHg), n (%)	71 (53)	137 (18)	35	<0.001
LA dilatation (LAVI >34 mL/m^2), n (%)	120 (85)	509 (63)	0	<0.001
LVSD (LVEF <40%), n (%)	51 (36)	318 (39)	0	0.49
Mitral regurgitation (≥moderate), n (%)	33 (24)	112 (14)	1	0.003
Tricuspid regurgitation (≥moderate), n (%)	41 (29)	44 (5)	0	<0.001

BMI= body mass index, BP= blood pressure, HR= heart rate, NYHA= New York Heart Association, SR = sinus rhythm, IHD = ischaemic heart disease, CVD = cerebrovascular disease, COPD= chronic obstructive pulmonary disease, Hb = Haemoglobin, NT-proBNP = N-terminal Pro Brain Natriuretic Peptide, MRA = Mineralocorticoid receptor antagonists, ACEi = Angiotensin-converting enzyme inhibitor, ARB = Angiotensin receptor blocker, BB= betablocker, GNRI = Geriatric nutritional risk index, LVEF= left ventricular ejection fraction, LAVI= left atrial volume index, TAPSE= tricuspid annular plane systolic excursion, IVC= inferior vena cava, RVSD= right ventricular systolic dysfunction, PAsP= pulmonary artery systolic pressure, RAP= right atrial pressure.

11.4.3 Prevalence of RVSD, increased PAsP and RAP

Compared to patients without HF, those with CHF were more likely to have RVSD, raised PAsP and raised RAP. In patients with CHF, 35% had raised RAP, 23% had raised PAsP and 38% had RVSD (Table 11.1b). RVSD and increased RAP were more common in

patients with HeFREF than in those with HeFNEF (Table 11.2b). Baseline characteristics by RVSD is shown in Table 11.4.

Table 11.4: Baseline characteristics of CHF patients by RVSD groups.

	RVSD		Missing	P
	Yes N=360	**No** N=592		
Demographics				
Age (years)	76 (70-82)	74 (66-81)	0	0.006
Sex (male), n (%)	262 (73)	393 (66)	0	0.04
BP systolic (mmHg)	121 (105-139)	130 (115-148)	0	<0.001
HR (bpm)	71 (62-81)	68 (60-76)	0	<0.001
Weight (kg)	77 (66-89)	82 (70-97)	0	<0.001
BMI (kg/m^2)	27 (24-31)	29 (25-33)	0	<0.001
NYHA III/IV, n (%)	156 (43)	161 (27)	0	<0.001
SR, n (%)	177 (49)	429 (73)	0	<0.001
Co-morbidities				
IHD, n (%)	241 (67)	338 (57)	0	0.003
HTN, n (%)	163 (45)	335 (57)	0	0.001
CVD, n (%)	37 (10)	53 (9)	0	0.50
Diabetes Mellitus, n (%)	106 (29)	179 (30)	0	0.80
COPD, n (%)	44 (12)	65 (11)	0	0.56
Medications				
ACEi/ARB, n (%)	302 (84)	503 (85)	0	0.66
BB, n (%)	458 (77)	278 (77)	0	0.96
MRA, n (%)	162 (45)	182 (31)	0	<0.001
Loop diuretics, n (%)	285 (79)	376 (64)	0	<0.001
Blood tests				
NT-proBNP (ng/L)	1926 (882-3907)	800 (364-1784)	1	<0.001
Hb (g/dL)	13.2 (12.0-14.2)	13.3 (12.1-14.4)	0	0.15
Sodium (mmol/L)	138 (136-140)	139 (137-140)	1	0.05

Table 11.4 (continued): Baseline characteristics of CHF patients by RVSD groups.

	RVSD		Missing	P
	Yes N=360	**No** N=592		
Blood tests				
Urea (mmol/L)	8.3 (6.1-11.3)	7.0 (5.3-9.7)	0	<0.001
Creatinine (umol/L)	109 (88-141)	100 (82-131)	0	0.27
Albumin (g/L)	38 (36-40)	38 (36-40)	0	0.07
Echocardiography				
Increased RAP (IVC ≥21 mm), n (%)	179 (51)	139 (24)	33	<0.001
Increased PAsP (Trans-tricuspid gradient ≥36mmHg), n (%)	126 (36)	82 (14)	35	<0.001
LA dilatation (LAVI >34 mL/m^2), n (%)	272 (76)	357 (60)	0	<0.001
LVSD (LVEF <40%), n (%)	184 (51)	185 (31)	0	<0.001
Mitral regurgitation (≥moderate), n (%)	86 (24)	59 (10)	1	<0.001
Tricuspid regurgitation (≥moderate), n (%)	63 (18)	22 (4)	0	<0.001
Clinical congestion				
Lung crackles (≥1)	58 (16)	62 (11)	0	0.01
Raised JVP (≥1)	79 (22)	46 (8)	0	<0.001
Peripheral oedema (≥1)	89 (25)	113 (19)	0	0.04
Palpable liver	33 (9)	18 (3)	0	<0.001
Congestion score (≥3)	81 (23)	60 (10)	0	<0.001
Malnutrition (GNRI)				
Normal (>98)	295 (82)	525 (89)	0	0.02
Mild (92-98)	51 (14)	47 (8)		
Moderate (82-91)	12 (3)	18 (3)		
Severe (<82)	2 (1)	2 (0)		

BMI= body mass index, BP= blood pressure, HR= heart rate, NYHA= New York Heart Association, SR = sinus rhythm, IHD = ischaemic heart disease, CVD = cerebrovascular disease, COPD= chronic obstructive pulmonary disease, Hb = Haemoglobin, NT-proBNP = N-terminal Pro Brain Natriuretic Peptide, MRA = Mineralocorticoid receptor antagonists, ACEi = Angiotensin-converting enzyme inhibitor, ARB = Angiotensin receptor blocker, BB= beta-blocker, GNRI = Geriatric nutritional risk index, LVEF= left ventricular ejection fraction, LAVI= left atrial volume index, TAPSE= tricuspid annular plane systolic excursion, IVC= inferior vena cava, RVSD= right ventricular systolic dysfunction, PAsP= pulmonary artery systolic pressure, RAP= right atrial pressure, JVP= jugular venous pressure.

11.4.4 Clinical associations of malnutrition

Compared to patients with normal nutritional status, patients with malnutrition were older, had lower BMI, worse renal function and HF symptoms, and higher NT-proBNP levels (Table 11.5).

Table 11.5: Baseline characteristics of CHF patients by malnutrition groups.

	Malnutrition		Missing	P
	Yes N=132	**No** N=820		
Demographics				
Age (years)	80 (74-84)	74 (66-80)	0	<0.001
Sex (male), n (%)	83 (63)	572 (70)	0	0.11
BP systolic (mmHg)	118 (103-138)	129 (112-146)	0	<0.001
HR (bpm)	70 (60-78)	70 (61-79)	0	0.73
Weight (kg)	59 (53-68)	84 (73-97)	0	<0.001
BMI (kg/m^2)	22 (20-24)	29 (26-33)	0	<0.001
NYHA III/IV, n (%)	60 (46)	257 (31)	0	0.001
SR, n (%)	89 (67)	517 (63)	0	0.33
Co-morbidities				
IHD, n (%)	84 (64)	495 (60)	0	0.48
HTN, n (%)	55 (42)	443 (54)	0	0.008
CVD, n (%)	14 (11)	76 (9)	0	0.63
Diabetes Mellitus, n (%)	23 (17)	262 (32)	0	0.001
COPD, n (%)	21 (16)	88 (11)	0	0.08
Medications				
ACEi/ARB, n (%)	99 (75)	706 (86)	0	0.001
BB, n (%)	102 (77)	634 (77)	0	0.99
MRA, n (%)	50 (38)	294 (36)	0	0.65
Loop diuretics, n (%)	98 (74)	563 (69)	0	0.20

Table 11.5 (continued): Baseline characteristics of CHF patients by malnutrition groups.

	Malnutrition		Missing	P
	Yes N=132	**No** N=820		
Blood tests				
NT-proBNP (ng/L)	2884 (1444-4973)	1015 (406-2089)	1	<0.001
Hb (g/dL)	12.4 (10.9-13.7)	13.3 (12.2-14.5)	0	<0.001
Sodium (mmol/L)	137 (135-140)	138 (137-140)	1	<0.001
Urea (mmol/L)	9.0 (6.4-12.6)	7.2 (5.4-9.9)	0	<0.001
Creatinine (umol/L)	114 (86-145)	102 (84 -132)	0	<0.001
Albumin (g/L)	35 (32-37)	39 (37-41)	0	<0.001
Echocardiography				
Increased RAP (IVC ≥21 mm), n (%)	64 (50)	254 (32)	33	<0.001
RVSD (TAPSE <17mm), n (%)	65 (49)	295 (36)	0	0.004
Increased PAsP (Trans-tricuspid gradient ≥36mmHg), n (%)	53 (41)	155 (20)	35	<0.001
LA dilatation (LAVI >34 mL/m^2), n (%)	94 (71)	535 (65)	0	0.18
LVSD (LVEF <40%), n (%)	61 (46)	308 (38)	0	0.06
Mitral regurgitation (≥moderate), n (%)	32 (24)	113 (14)	1	0.002
Tricuspid regurgitation (≥moderate), n (%)	28 (21)	57 (7)	0	<0.001
Clinical congestion				
Lung crackles (≥1)	28 (21)	92 (11)	0	0.001
Raised JVP (≥1)	31 (24)	94 (12)	0	<0.001
Peripheral oedema (≥1)	40 (30)	162 (20)	0	0.006
Palpable liver	17 (13)	34 (4)	0	<0.001
Congestion score (≥3)	36 (27)	105 (13)	0	<0.001

BMI= body mass index, BP= blood pressure, HR= heart rate, NYHA= New York Heart Association, SR = sinus rhythm, IHD = ischaemic heart disease, CVD = cerebrovascular disease, COPD= chronic obstructive pulmonary disease, Hb = Haemoglobin, NT-proBNP = N-terminal Pro Brain Natriuretic Peptide, MRA = Mineralocorticoid receptor antagonists, ACEi = Angiotensin-converting enzyme inhibitor, ARB = Angiotensin receptor blocker, BB= betablocker, GNRI = Geriatric nutritional risk index, LVEF= left ventricular ejection fraction, LAVI= left atrial volume index, TAPSE= tricuspid annular plane systolic excursion, IVC= inferior vena cava, RVSD= right ventricular systolic dysfunction, PAsP= pulmonary artery systolic pressure, RAP= right atrial pressure, JVP= jugular venous pressure.

Malnutrition and clinical signs of congestion

CHF patients with malnutrition were more likely to have signs of congestion on clinical examination than those without malnutrition. Of the 4 clinical signs of congestion, peripheral oedema and raised JVP were the two commonest (Table 11.5). Malnourished patients with HeFREF or HeFNEF were equally likely to have signs of congestion (Table 11.6a-b).

Table 11.6a: Baseline characteristics of HeFREF patients by GNRI categories.

	GNRI			P
	Normal (<98)	**Mild** (92-98)	**≥ Mod** (≤91)	
	N=308	N=51	N=10	
Demographics				
Age (years)	72 (64-78)	77 (72-82)	78 (64-83)	0.001
Sex (male), n (%)	240 (78)	31 (61)	8 (80)	0.03
BP systolic (mmHg)	120 (105-138)	112 (97-132)	117 (101-133)	0.21
HR (bpm)	70 (61-78)	70 (64-79)	79 (70-90)	0.05
Weight (kg)	83 (74-93)	64 (57-71)	56 (46-58)	<0.001
BMI (kg/m^2)	28 (26-31)	23 (21-24)	21 (19-21)	<0.001
NYHA III/IV, n (%)	107 (35)	25 (49)	5 (50)	0.09
SR, n (%)	229 (74)	38 (75)	6 (60)	0.59
Co-morbidities				
IHD, n (%)	220 (71)	41 (80)	3 (30)	0.005
HTN, n (%)	127 (41)	22 (43)	2 (20)	0.38
CVD, n (%)	24 (8)	4 (8)	0	0.66
Diabetes Mellitus, n (%)	86 (28)	12 (24)	0	0.13
COPD, n (%)	31 (10)	6 (12)	4 (40)	0.01
Medications				
ACEi/ARB, n (%)	285 (93)	44 (86)	8 (80)	0.15
BB, n (%)	261 (85)	45 (88)	6 (60)	0.08
MRA, n (%)	158 (51)	27 (53)	6 (60)	0.85
Loop diuretics, n (%)	227 (74)	41 (80)	8 (80)	0.55

Table 11.6a (continued): Baseline characteristics of HeFREF patients by GNRI categories.

	GNRI			P
	Normal (<98)	**Mild** (92-98)	**≥ Mod** (≤91)	
	N=308	N=51	N=10	
Blood tests				
NT-proBNP (ng/L)	1421 (624-3046)	3543 (2013-6342)	3467 (933-9353)	<0.001
Hb (g/dL)	13.5 (12.4-14.3)	12.5 (11.0-13.9)	13.7 (12.0-14.6)	0.001
Sodium (mmol/L)	139 (137-140)	138 (136-140)	135 (134-138)	<0.001
Urea (mmol/L)	7.3 (5.7-9.8)	8.5 (6.4-11.1)	8.0 (2.9-12.7)	0.20
Creatinine (umol/L)	106 (85-136)	112 (87-141)	112 (62-187)	0.86
Albumin (g/L)	39 (37-41)	35 (33-37)	34 (30-34)	<0.001
Echocardiography				
IVC diameter (mm), n (%)	18 (16-23)	22 (18-25)	22 (14-25)	0.01
RVSD (TAPSE <17mm), n (%)	147 (48)	31 (61)	6 (60)	0.18
Trans-tricuspid gradient (mmHg), n (%)	25 (20-33)	33 (23-41)	24 (16-30)	<0.001
LAVI (mL/m^2), n (%)	45.0 (32.8-56.4)	49.8 (35.0-64.2)	49.6 (17.8-59.2)	0.14
LVEF (%), n (%)	32 (27-36)	28 (24-35)	28 (22-35)	0.01
Mitral regurgitation (≥moderate), n (%)	56 (18)	14 (27)	1 (10)	0.02
Tricuspid regurgitation (≥moderate), n (%)	18 (6)	7 (14)	3 (30)	0.007
Clinical congestion				
Lung crackles (≥1)	29 (9)	10 (20)	4 (40)	0.002
Raised JVP (≥1)	40 (13)	9 (18)	3 (30)	0.23
Peripheral oedema (≥1)	46 (15)	17 (34)	2 (20)	0.006
Palpable liver	10 (3)	7 (14)	1 (10)	0.004
Congestion score (≥3)	35 (11)	13 (26)	3 (30)	0.008

Table 11.6b: Baseline characteristics of HeFNEF patients by GNRI categories.

	GNRI			P
	Normal (<98)	**Mild** (92-98)	**≥ Mod** (≤91)	
	N=512	N=47	N=24	
Demographics				
Age (years)	75 (67-82)	80 (77-86)	81 (78-85)	<0.001
Sex (male), n (%)	332 (65)	31 (66)	13 (54)	0.55
BP systolic (mmHg)	133 (118-152)	123 (106-142)	115 (107-131)	0.001
HR (bpm)	69 (60-79)	69 (60-74)	68 (59-76)	0.69
Weight (kg)	84 (72-99)	59 (54-68)	55 (48-68)	<0.001
BMI (kg/m^2)	30 (27-34)	22 (20-24)	21 (19-22)	<0.001
NYHA III/IV, n (%)	150 (29)	20 (42)	10 (42)	0.24
SR, n (%)	288 (56)	24 (51)	21 (88)	0.007
Co-morbidities				
IHD, n (%)	275 (54)	29 (62)	11 (46)	0.41
HTN, n (%)	316 (62)	21 (45)	10 (42)	0.01
CVD, n (%)	52 (10)	7 (15)	3 (13)	0.58
Diabetes Mellitus, n (%)	176 (34)	7 (15)	4 (17)	0.006
COPD, n (%)	57 (11)	7 (15)	4 (17)	0.55
Medications				
ACEi/ARB, n (%)	421 (82)	32 (68)	15 (63)	0.005
BB, n (%)	373 (73)	37 (79)	14 (58)	0.19
MRA, n (%)	136 (27)	13 (28)	4 (17)	0.55
Loop diuretics, n (%)	336 (66)	29 (62)	20 (83)	0.16
Blood tests				
NT-proBNP (ng/L)	776 (347-1717)	2148 (1065-4274)	3171 (666-4905)	<0.001
Hb (g/dL)	13.3 (12.1-14.5)	12.4 (11.2-13.4)	11.4 (9.7-12.8)	<0.001
Sodium (mmol/L)	138 (137-140)	138 (136-140)	136 (132-140)	0.001
Urea (mmol/L)	7.1 (5.3-10.0)	9.2 (6.8-13.9)	9.2 (5.1-15.2)	<0.001
Creatinine (umol/L)	101 (83-131)	116 (92-165)	111 (83-144)	0.10
Albumin (g/L)	39 (37-40)	36 (34-38)	30 (29-35)	<0.001

Table 11.6b (continued): Baseline characteristics of HeFNEF patients by GNRI categories.

	GNRI			P
	Normal (<98) N=512	**Mild** (92-98) N=47	**≥ Mod** (≤91) N=24	
Echocardiography				
IVC diameter (mm), n (%)	18 (16-21)	20 (17-23)	19 (15-23)	0.07
RVSD (TAPSE <17mm), n (%)	148 (29)	20 (43)	8 (33)	0.14
Trans-tricuspid gradient (mmHg), n (%)	25 (20-31)	30 (23-45)	30 (25-44)	<0.001
LAVI (mL/m^2), n (%)	39.7 (28.0-52.4)	46.3 (35.4-68.5)	33.3 (25.8-50.1)	0.02
LVEF (%), n (%)	53 (46-60)	54 (46-63)	54 (43-60)	0.75
Mitral regurgitation (≥moderate), n (%)	57 (11)	10 (21)	7 (29)	0.001
Tricuspid regurgitation (≥moderate), n (%)	39 (8)	10 (21)	8 (33)	<0.001
Clinical congestion				
Lung crackles (≥1)	63 (12)	9 (19)	5 (21)	0.22
Raised JVP (≥1)	54 (11)	11 (23)	8 (33)	<0.001
Peripheral oedema (≥1)	116 (23)	14 (30)	7 (29)	0.76
Palpable liver	24 (5)	4 (9)	5 (21)	0.003
Congestion score (≥3)	70 (14)	11 (23)	9 (38)	0.002

HeFREF= heart failure with reduced ejection fraction, HeFNEF= heart failure with normal ejection fraction, BMI= body mass index, BP= blood pressure, HR= heart rate, JVP= jugular venous pressure, NYHA = New York Heart Association, SR = sinus rhythm, IHD = ischaemic heart disease, CVD = cerebrovascular disease, COPD= chronic obstructive pulmonary disease, Hb = Haemoglobin, NT-proBNP = N-terminal Pro Brain Natriuretic Peptide, MRA = Mineralocorticoid receptor antagonists, ACEi = Angiotensin-converting enzyme inhibitor, ARB = Angiotensin receptor blocker, BB= betablocker, LVEF= left ventricular ejection fraction, TAPSE= tricuspid annular plane systolic excursion, RVSD= right ventricular systolic dysfunction, LAVI= left atrial volume index, GNRI = Geriatric nutritional risk index, Mod = moderate.

Malnutrition and echocardiography

Patients with malnutrition were more likely to have RVSD and increased PAsP and RAP compared to those with normal nutrition. (Table 11.5) The simultaneous presence of RVSD and increased RAP was much more common in malnourished patients than in non-malnourished patients (33% vs 17%, P<0.001). The prevalence of LV systolic dysfunction and LA dilation was not related to malnutrition (Table 11.5). Box plot figures

comparing the key echocardiographic measures in malnourished vs non-malnourished patients with HeFREF and HeFNEF were shown in Figures 11.1a-e.

Figure 11.1a: IVC diameter in malnourished vs non-malnourished patients with HeFREF and HeFNEF.

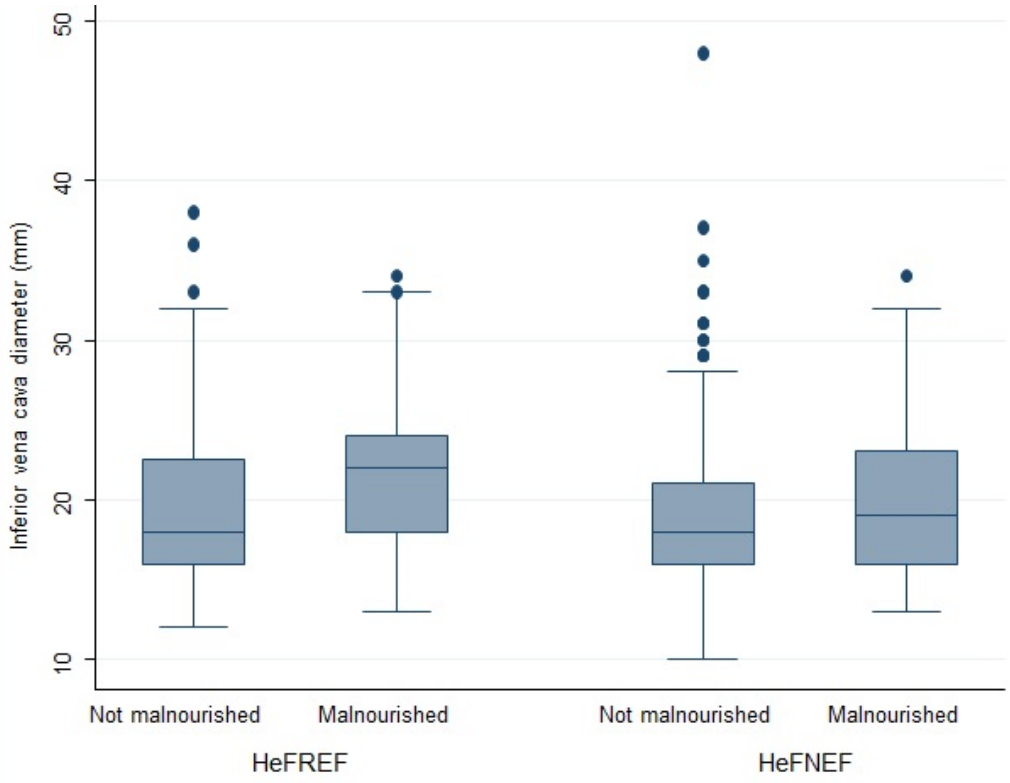


Figure 11.1b: TAPSE in malnourished vs non-malnourished patients with HeFREF and HeFNEF.

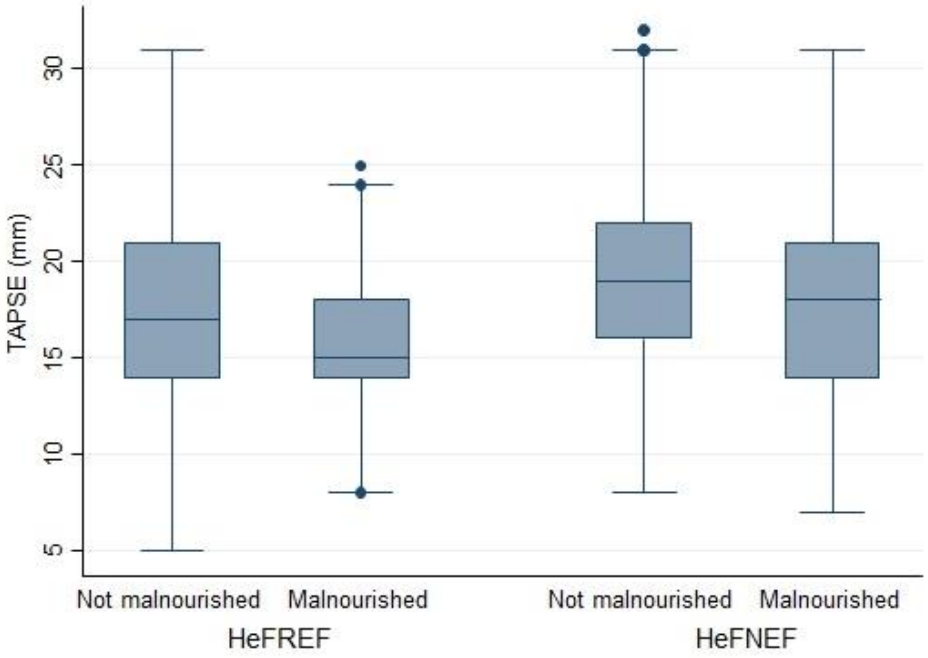


Figure 11.1c: Trans-tricuspid gradient in malnourished vs non-malnourished patients with HeFREF and HeFNEF.

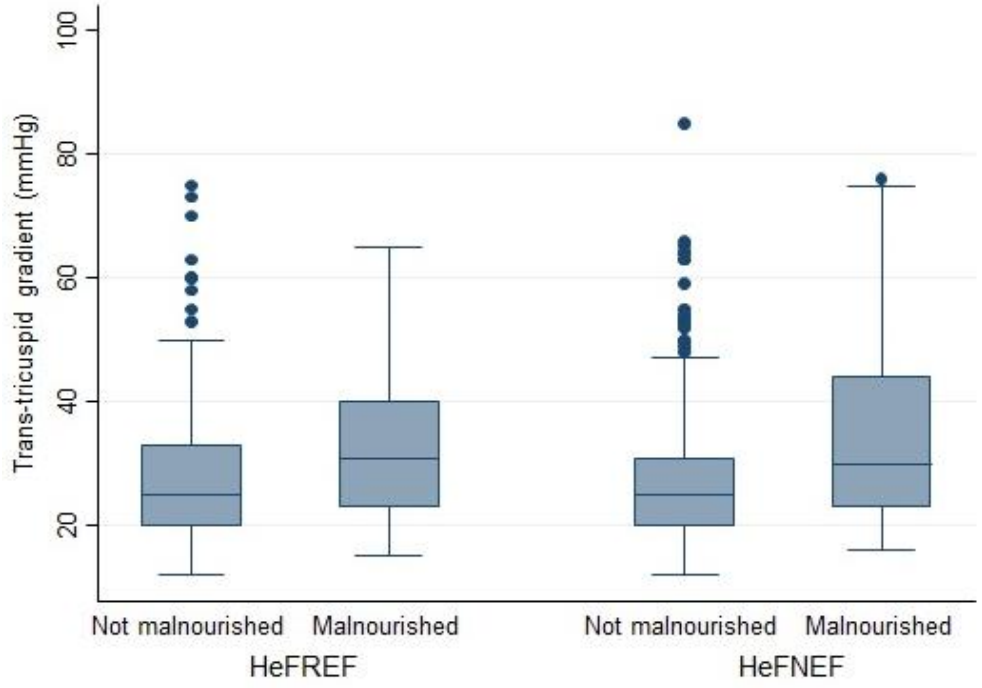


Figure 11.1d: LVEF in malnourished vs non-malnourished patients with HeFREF and HeFNEF.

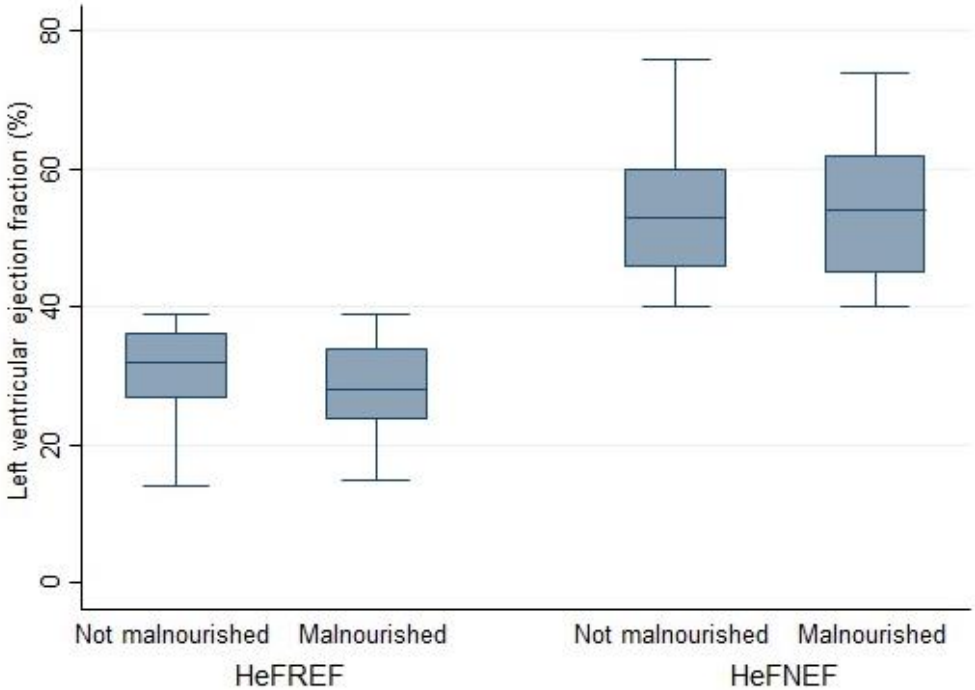
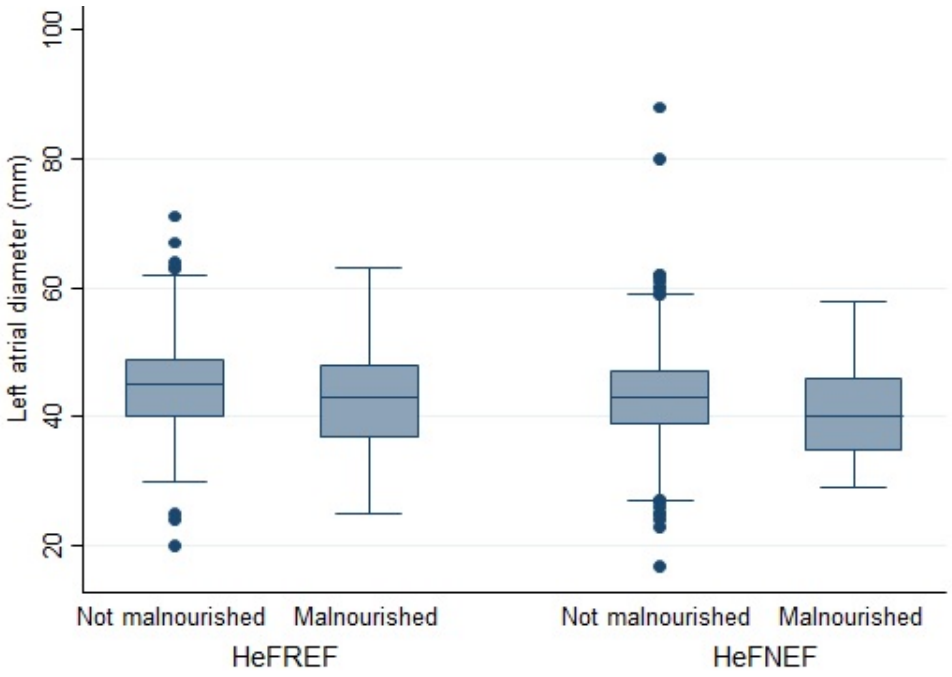


Figure 11.1e: LA diameter in malnourished vs non-malnourished patients with HeFREF and HeFNEF.



IVC = inferior vena cava; TAPSE = tricuspid annular plane systolic excursion; LVEF= left ventricular ejection fraction, LA = left atrial; HeFREF = heart failure with reduced ejection fraction; HeFNEF= heart failure with normal ejection fraction.

11.4.5 Correlations between malnutrition and echocardiographic findings

Worsening malnutrition correlated with increasing NT-proBNP, increasing age and worsening RV dysfunction by ultrasound: decreasing TAPSE, increasing RAP and PAsP (Table 11.7). Malnutrition was more strongly linked to elevated right-sided pressures and RVSD than LV dysfunction (Table 11.7).

If an NT-proBNP cut-off of >400 ng/L was used to diagnose HeFNEF, in accordance to the NICE guidelines (10), the prevalence of congestion and malnutrition would have been slightly higher amongst patients with HeFNEF (congestion score ≥3: from 15% to 18%; RVSD: from 30% to 34%, malnutrition from 12% to 15%). However, the change in cut-off did not alter the modest relationship between congestion, RVSD and malnutrition (worsening malnutrition correlated with decreasing TAPSE (correlation coefficient from

0.21 to 0.17 (both P<0.001) and increasing congestion score (correlation coefficient remains the same: 0.05, P=0.15 and P=0.16 respectively).

Table 11.7: Correlation between clinical or echocardiographic variables and malnutrition in CHF patients.

	GNRI (decreasing GNRI = worse malnutrition)	
	r	**P**
Clinical variables of advanced HF		
Age (years)	-0.36	<0.001
NT-proBNP (ng/L)	-0.41	<0.001
Echocardiographic variable		
LVEF (%)	0.12	<0.001
LVEDD (mm)	0.06	0.08
LVEDV (mL)	0.01	0.75
LVESV(mL)	-0.04	0.19
TAPSE (mm)	0.21	<0.001
LA diameter (mm)	-0.13	<0.001
LA volume (mL)	-0.01	0.67
LAVI (mL/m^2)	-0.15	<0.001
Tricuspid regurgitation (≥mod)	-0.16	<0.001
Trans-tricuspid gradient (mmHg)	-0.26	<0.001
TR Vmax (m/s)	-0.26	<0.001
IVC diameter (mm)	-0.15	<0.001
GLS (%)	-0.12	0.003
E/e’	-0.13	0.02

LVEF= left ventricular ejection fraction, LVEDD= left ventricular end diastolic diameter, LVEDV = left ventricular end diastolic volume, LVESV = left ventricular end systolic volume, TAPSE= tricuspid annular plane systolic excursion, LA= Left atrial, LAVI= left atrial volume index, TR Vmax = maximal tricuspid regurgitation velocity, IVC = inferior vena cava, GLS= left ventricular global longitudinal strain, E/e’ = ratio between early mitral inflow velocity and mitral annular early diastolic velocity, GNRI = Geriatric nutritional risk index, *r*= correlation coefficient

Logistic regression analysis of clinical and echocardiographic variables associated with malnutrition is shown in Table 11.8. Log [NT-proBNP] (OR 5.7, 95% CI 3.2-10.1, P<0.001) had the strongest association with malnutrition, followed by trans-tricuspid gradient (OR 1.11, 95% CI 1.0-1.2, P=0.03) (Table 11.8).

Table 11.8: Logistic regression analysis (backward selection) of clinical and echocardiographic variables associated with malnutrition in CHF patients.

	Univariable			Multivariable		
	OR (95% CI)	χ^2	P	OR (95% CI)	χ^2	P
Age	1.06 (1.04-1.08)	27.4	<0.001	1.03 (1.01-1.06)	7.9	0.005
Log [NT-proBNP]	6.15 (4.04-9.36)	71.8	<0.001	5.68 (3.20-10.06)	35.4	<0.001
LVEF (per 5% increase)	0.93 (0.86-0.99)	4.8	0.03			
LAVI (per 10 mL/m^2 increase)	1.10 (1.02-1.19)	5.8	0.02			
TAPSE (per 5mm increase)	0.69 (0.56-0.85)	12.4	<0.001			
Trans-tricuspid gradient (per 5 mmHg increase)	1.24 (1.15-1.33)	32.5	<0.001	1.11 (1.01-1.22)	4.7	0.03
IVC diameter (per 5 mm increase)	1.42 (1.18-1.71)	14.0	<0.001			

NYHA = New York Heart Association, NT-proBNP = N-terminal Pro Brain Natriuretic Peptide, LVEF = left ventricular ejection fraction, LAVI = left atrial volume index, IVC = inferior vena cava, TAPSE = tricuspid annular plane systolic excursion, OR = odds ratio, CI = confidence interval, $\chi 2$ = chi-square.

11.4.6 Malnutrition, echocardiographic findings and hospitalisation in the year before recruitment

539 (57%) of patients were admitted to hospital in the year before recruitment, of whom 181 (34%) had HF admissions. Patients with previous hospitalisations for HF were more

likely to be malnourished and have raised RAP / PAsP or RVSD compared to patients with previous cardiovascular but non-HF hospitalisations or no hospitalisations (Table 11.9).

Table 11.9: Relationship between hospitalisation in the year before recruitment and malnutrition and raised RAP, PAsP or RVSD at baseline. (Expressed as number of patients (%))

	Number of hospitalisations in the year before recruitment					
	≥1 (N=539)				None (N=413)	
	HF hosp (N=181)		Non-HF hosp (N=358)			
	Mal (N=36)	Not Mal (N=145)	Mal (N=55)	Not Mal (N=303)	Mal (N=41)	Not Mal (N=372)
↑ RAP (IVC ≥21mm)	23 (13)	57 (31)	26 (8)	95 (28)	15 (4)	102 (25)
↑ PAsP (trans-tricuspid gradient ≥ 36mmHg)	18 (10)	44 (24)	19 (6)	50 (14)	16 (4)	61 (15)
RVSD (TAPSE <17mm)	27 (15)	67 (37)	24 (7)	107 (30)	14 (3)	121 (29)

RAP = right atrial pressure, PAsP = pulmonary arterial systolic pressure, RVSD = right ventricular systolic dysfunction, IVC = inferior vena cava, TAPSE= tricuspid annular plane systolic excursion, hosp = hospitalisation, mal = malnourished.

11.4.7 Malnutrition, RVSD and mortality

During a median follow-up of 1683 (IQR: 1096-2230) days, 461 (44%) patients died.

Univariable and multivariable predictors of mortality for the overall CHF population and for the different HF phenotypes are shown in table 11.10 and tables 11.11a-b. In univariable analysis, the presence of malnutrition, signs of congestion, increasing PASP, RAP and LAVI and decreasing TAPSE and LVEF, were associated with worse outcome.

Table 11.10: Univariable and multivariable analyses of factors predicting all-cause mortality in CHF patients.

Worse outcome per unitary increase	Univariable			Multivariable		
	HR (95%CI)	χ^2	P	HR (95%CI)	χ^2	P
Age (years)	1.05 (1.04-1.06)	97.2	*	1.04 (1.03-1.06)	43.5	*
Sex (male vs female)	1.20 (0.98-1.47)	3.0	0.08	1.46 (1.14-1.85)	9.3	0.002
BP systolic (per 10 mmHg)	0.92 (0.89-0.96)	16.3	*	0.94 (0.90-0.98)	9.1	0.003
HR (bpm)	1.01 (1.00-1.01)	4.1	0.04			
SR (Y vs N)	0.78 (0.65-0.94)	6.6	0.01	0.71 (0.55-0.91)	7.5	0.006
NYHA (III/IV vs I/II)	2.65 (2.20-3.18)	108.3	*	1.61 (1.31-1.99)	20.1	*
Congestion score (≥3 vs <3)	2.77 (2.23-3.43)	85.5	*			
IHD (Y vs N)	1.23 (1.01-1.49)	4.3	0.04			
CVD (Y vs N)	1.76 (1.35-2.30)	17.3	*	1.41 (1.06-1.89)	5.5	0.02
Log [NT-proBNP]	3.48 (2.89-4.18)	175.9	*	1.49 (1.13-1.96)	8.0	0.005
Hb (g/dL)	0.78 (0.74-0.82)	86.6	*			
Urea (mmol/L)	1.08 (1.06-1.09)	91.3	*			
Sodium (mmol/L)	0.93 (0.90-0.96)	27.5	*	0.96 (0.93-0.99)	9.2	0.002
LVEF (%)	0.99 (0.99-1.00)	4.6	0.03			
LVEDD (mm)	1.01 (1.00-1.02)	2.7	0.10			
TAPSE (mm)	0.93 (0.91-0.95)	48.4	*			
LAVI (mL/m^2)	1.02 (1.01-1.02)	87.8	*	1.01 (1.00-1.01)	5.8	0.02
Trans-tricuspid gradient (mmHg)	1.03 (1.03-1.04)	84.0	*			
IVC diameter (mm)	1.09 (1.08-1.11)	98.6	*	1.04 (1.01-1.06)	5.6	0.02
GNRI (≥mod vs < mod)	1.75 (1.14-2.68)	6.5	0.01	2.32 (1.49-3.62)	13.8	*

*P<0.001. Lung crackles, raised JVP, peripheral oedema, palpable liver are excluded as these are included in congestion score. Weight and BMI are excluded as these are included in GNRI. GLS and e/e' are excluded due to large amount of missing values.

BP= blood pressure, HR= heart rate, NYHA = New York Heart Association, SR = sinus rhythm, IHD = ischaemic heart disease, CVD = cerebrovascular disease, Hb = Haemoglobin, NT-proBNP = N-terminal Pro Brain Natriuretic Peptide, LVEF= left ventricular ejection fraction, LVEDD= left ventricular end diastolic diameter, TAPSE= tricuspid annular plane systolic excursion, LAVI= left atrial volume index, IVC = inferior vena cava, Mod= moderate, GNRI = Geriatric nutritional risk index, Y= yes, N=No, HR = hazard ratio, CI= confidence interval, χ^2= chi-square.

Table 11.11a: Univariable and multivariable analyses of factors predicting all-cause mortality in HeFREF patients.

Worse outcome per unitary increase	Univariable			Multivariable		
	HR (95%CI)	χ^2	P	HR (95%CI)	χ^2	P
Age (years)	1.05 (1.04-1.07)	40.6	*	1.04 (1.02-1.06)	15.7	*
Sex (male vs female)	1.29 (0.91-1.83)	2.1	0.15			
BP systolic (per 10 mmHg)	0.90 (0.84-0.96)	9.4	0.002	0.90 (0.83-0.97)	8.0	0.005
HR (bpm)	1.01 (1.00-1.02)	1.4	0.23			
SR (Y vs N)	0.81 (0.59-1.12)	1.6	0.21			
NYHA (III/IV vs I/II)	2.22 (1.67-2.96)	29.4	*	1.63 (1.18-2.26)	8.6	0.003
Congestion score (≥3 vs <3)	2.50 (1.76-3.55)	26.1	*			
IHD (Y vs N)	1.56 (1.10-2.20)	6.3	0.01	1.55 (1.06-2.26)	5.0	0.03
CVD (Y vs N)	1.33 (0.83-2.14)	1.4	0.24			
Log [NT-proBNP]	3.47 (2.56-4.69)	64.8	*	1.66 (1.05-2.63)	4.6	0.03
Hb (g/dL)	0.83 (0.76-0.91)	17.3	*			
Urea (mmol/L)	1.07 (1.05-1.09)	34.4	*			
Sodium (mmol/L)	0.94 (0.90-0.99)	6.9	0.009			
LVEF (%)	0.96 (0.94-0.98)	14.6	*			
LVEDD (mm)	1.00 (0.99-1.03)	0.9	0.35			
TAPSE (mm)	0.94 (0.91-0.97)	12.8	*			
LAVI (mL/m^2)	1.02 (1.01-1.02)	29.4	*			
Trans-tricuspid gradient (mmHg)	1.04 (1.02-1.05)	35.9	*			
IVC diameter (mm)	1.08 (1.05-1.11)	31.8	*			
GNRI (≥mod vs < mod)	2.34 (1.13-4.85)	5.3	0.02	4.00 (1.83-8.76)	12.1	0.001

Table 11.11b: Univariable and multivariable analyses of factors predicting all-cause mortality in HeFNEF patients.

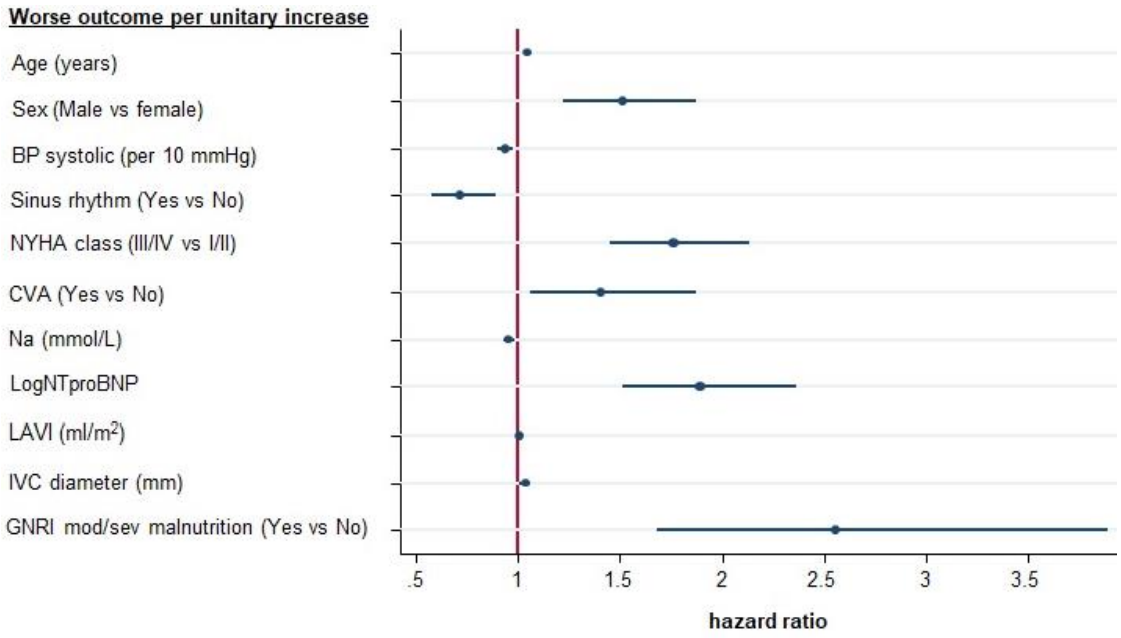
Worse outcome per unitary increase	Univariable			Multivariable		
	HR (95%CI)	χ^2	P	HR (95%CI)	χ^2	P
Age (years)	1.06 (1.05-1.07)	66.5	*	1.04 (1.02-1.05)	18.7	*
Sex (male vs female)	1.12 (0.87-1.44)	0.8	0.38			
BP systolic (per 10 mmHg)	0.94 (0.90-0.99)	5.8	0.02	0.94 (0.89-0.98)	7.0	0.008
HR (bpm)	1.00 (1.00-1.01)	1.1	0.30			
SR (Y vs N)	0.72 (0.57-0.92)	6.9	0.009	0.70 (0.51-0.97)	4.7	0.03
NYHA (III/IV vs I/II)	2.53 (1.99-3.22)	56.7	*	1.57 (1.19-2.06)	10.4	0.001
Congestion score (≥3 vs <3)	2.59 (1.96-3.43)	44.7	*			
IHD (Y vs N)	1.05 (0.83-1.34)	0.2	0.68			
CVD (Y vs N)	2.07 (1.50-2.86)	19.3	*	1.43 (1.01-2.05)	4.0	0.05
Log [NT-proBNP]	3.72 (2.91-4.74)	111.7	*	1.67 (1.19-2.36)	8.7	0.003
Hb (g/dL)	0.77 (0.72-0.82)	56.7	*			
Urea (mmol/L)	1.08 (1.06-1.10)	56.7	*			
Sodium (mmol/L)	0.93 (0.90-0.96)	16.8	*	0.96 (0.92-0.99)	5.2	0.02
LVEF (%)	1.00 (0.99-1.02)	0.3	0.57			
LVEDD (mm)	1.00 (0.99-1.02)	0.06	0.80			
TAPSE (mm)	0.92 (0.90-0.95)	34.0	*			
LAVI (mL/m^2)	1.02 (1.01-1.02)	56.3	*	1.01 (1.00-1.02)	7.6	0.006
Trans-tricuspid gradient (mmHg)	1.03 (1.03-1.04)	48.4	*			
IVC diameter (mm)	1.10 (1.01-1.13)	67.2	*	1.05 (1.01-1.09)	6.6	0.01
GNRI (≥mod vs < mod)	1.66 (0.95-2.90)	3.2	0.08	1.93 (1.12-3.32)	5.6	0.02

*P<0.001. Lung crackles, raised JVP, peripheral oedema, palpable liver are excluded as these are included in congestion score. Weight and BMI are excluded as these are included in GNRI. GLS and e/e' are excluded due to large amount of missing values.

HeFREF = heart failure with reduced ejection fraction, HeFNEF = heart failure with normal ejection fraction, BP= blood pressure, HR= heart rate, NYHA = New York Heart Association, SR = sinus rhythm, IHD = ischaemic heart disease, CVD = cerebrovascular disease, Hb = Haemoglobin, NT-proBNP = N-terminal Pro Brain Natriuretic Peptide, LVEF= left ventricular ejection fraction, LVEDD= left ventricular end diastolic diameter, TAPSE= tricuspid annular plane systolic excursion, LAVI= left atrial volume index, IVC = inferior vena cava, Mod= moderate, GNRI = Geriatric nutritional risk index, Y= yes, N=No, HR = hazard ratio, CI= confidence interval, χ^2= chi-square.

In a multivariable model including all CHF patients, malnutrition was independently associated with an increased risk of all-cause mortality. Of the echocardiographic variables, only increasing RAP and LAVI were significant predictors of mortality (Table 11.10, Figure 11.2).

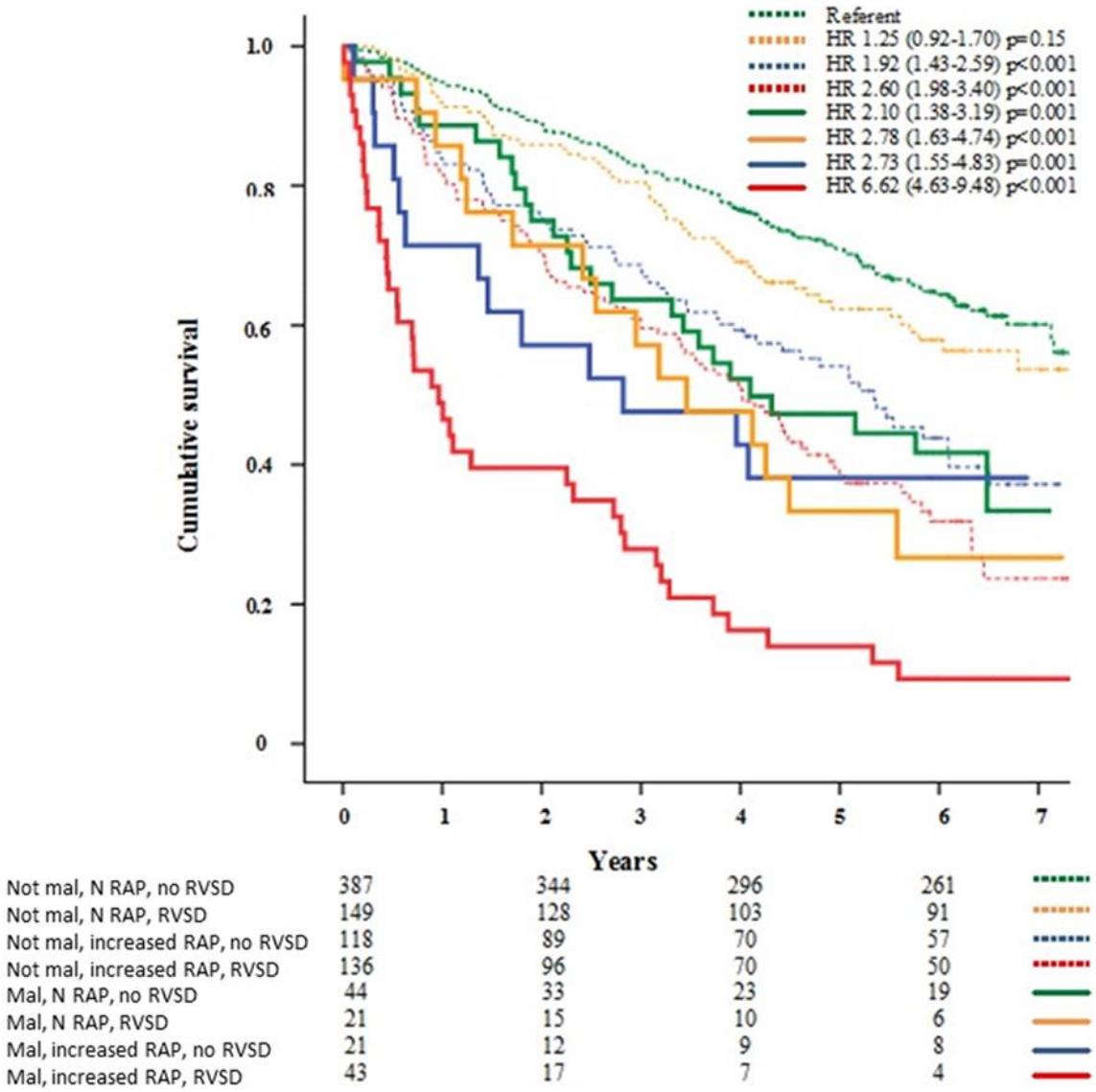
Figure 11.2: Forest plot on multivariable analysis of factors predicting all-cause mortality in CHF patients.



BP = blood pressure, NYHA = New York Heart Association, CVA = cerebrovascular disease, Na = sodium, NT-proBNP = N-terminal pro brain natriuretic peptide, LAVI = left atrial volume index, IVC = inferior vena cava, mod/sev = moderate or severe, GNRI = geriatric nutritional risk index.

The Kaplan-Meier curves for the relationship between malnutrition, RVSD, increased RAP and outcome is shown in Figure 11.3. Compared to patients who were not malnourished with normal RV function and RAP, those with malnutrition and normal RV function and RAP had a 2-fold increase in the risk of death for any cause. Those who were malnourished with RVSD and raised RAP had the worst outcome (Figure 11.3).

Figure 11.3: Kaplan Meier curves illustrating the relation amongst malnutrition, RVSD, increased RAP and all-cause mortality.



Mal = malnutrition, N= normal, RAP = right atrial pressure, RVSD = right ventricular systolic dysfunction, HR = Hazard ratio.

A base model (including age, systolic BP, NYHA class, urea and log [NT-proBNP]) for predicting mortality achieved a C-index = 0.79 (Table 11.12). Moderate to severe malnutrition by GNRI and markers of congestion (both clinical and echocardiographic), when added individually, did not improve performance of the base model. The net

reclassification index (NRI) produced similar results. Addition of moderate to severe malnutrition by GNRI and clinical congestion (congestion score ≥3) in combination and addition of moderate to severe malnutrition by GNRI and IVC diameter in combination improved performance of base model (C = 0.80 and 0.81 respectively, P=0.02 for both).

Table 11.12: Addition of clinical congestion and echocardiographic markers of right cardiac dysfunction and their impact on performance of base model in predicting all-cause mortality.

Model	Harrell's C-statistic (Compared to base)	Harrell's C-statistic (Compared to model 6)	cNRI (Standard error) (Compared to base)
1. Base model*	0.789 (0.754-0.823)	-	-
2. Base + clinical congestion**	0.796 (0.762-0.830) P=0.10	-	0.03 (0.08) P=0.69
3. Base + TAPSE	0.789 (0.750-0.820) P=0.83	-	0.013 (0.08) P=0.87
4. Base + IVC	0.796 (0.760-0.830) P=0.18	-	0.14 (0.08) P=0.07
5. Base + Trans-tricuspid gradient	0.791 (0.756-0.826) P=0.60	-	-0.0003 (0.08) P=1.0
6. Base + GNRI***	0.797 (0.762-0.831) P=0.12	0.797 (0.762-0.831)	0.08 (0.08) P=0.29
7. Base + GNRI*** + clinical congestion	0.800 (0.770-0.840) P=0.02	0.803 (0.770-0.837) P=0.08	-
8. Base + GNRI*** + IVC	0.807 (0.770-0.840) P=0.02	0.807 (0.772-0.832) P=0.08	-
9. Base + GNRI*** + TAPSE	0.797 (0.760-0.830) P=0.11	0.797 (0.763-0.831) P=0.78	-
10. Base + GNRI*** + Trans-tricuspid gradient	0.798 (0.760-0.830) P=0.12	0.798 (0.763-0.833) P=0.78	-

*Variables included in the base model include: age, systolic BP, NYHA class, urea and log[NT-proBNP]. ** Clinical congestion (congestion score ≥3 vs <3), ***GNRI (≥ moderate vs < moderate malnutrition)

TAPSE= tricuspid annular plane systolic excursion, IVC=inferior vena cava diameter, GNRI = geriatric nutritional risk index, NRI= net reclassification index.

11.5 Discussion

This study is one of the few studies (92, 199, 203) to explore the relation between malnutrition and congestion in patients with CHF. This study comprehensively investigated the associations between malnutrition, right heart dysfunction and venous congestion assessed clinically, biochemically and by echocardiography.

I hypothesised that malnutrition might be caused by congestion, but only found a modest relation between malnutrition and measures of congestion. Although this study is a study of associations of malnutrition, and thus few conclusions can be drawn about causation, the weakness of the correlation between the two suggests that one does not directly cause the other. Congestion and malnutrition were independent predictors of mortality, again suggesting that they are measures of different aspects of the HF syndrome and may not be causally related.

One explanation for our findings might be that it is *historical* congestion that causes malnutrition and that the malnutrition measured at the time of assessment would not be related to any congestion present at the time. An interesting finding was that patients with previous admissions for HF were more likely to be malnourished and have raised RAP/ PAsP or RVSD compared to patients with previous cardiovascular but non-HF hospitalisations or no hospitalisations, which might imply a closer link between malnutrition and previous congestion.

Our findings are similar to those from Valentova et al, who studied the relationship between congestion and cardiac cachexia in 169 outpatients with HF due to LVSD (92). They found that cachexia was more common in patients with reduced RV function and elevated RAP than in patients with either reduced RV function but normal RAP or preserved RV function (67 vs. 15 vs. 7%). They also found that cachexia was associated with thicker bowel walls.

Previous work has mainly focused on identifying mechanistically plausible explanations for the association between cachexia/ malnutrition and congestion/cardiac dysfunction in patients with CHF. Congestion and cardiac dysfunction have been implicated as a cause of malnutrition. Systemic venous congestion in the hepatic and splanchnic beds cause intestinal congestion and dysmotility, anorexia, malabsorption and increased intestinal

permeability with protein loss and endotoxin translocation (204). Neuro-hormonal activation exacerbates renal dysfunction, leading to more salt and water retention, contributing to bowel congestion and development of malnutrition (111). Chronic intestinal congestion might cause persistent lipopolysaccharide translocation which might induce systemic release of pro-inflammatory cytokines and worsen the underlying intestinal congestion (92). In addition, RV dysfunction and pulmonary hypertension cause release of natriuretic peptides (205), which stimulates lipolysis of adipose tissue (206) and indirectly stimulate secretion of adiponectin which promotes glucose and fatty acid utilisation (207), resulting in weight loss and increased mortality.

Malnutrition might itself aggravate underlying left and right heart dysfunction, leading to a vicious spiral of deterioration. Metabolites and cytokines released secondary to a malnourishment state might adversely affect cardiac performance. Cytokines such as TNF-α, are raised in patients with cachexia; they have potent negative inotropic effects and might subsequently impair RV and LV systolic function (208).

Although this study showed that malnutrition was associated with congestion, the association was modest, suggesting that they are two distinct entities. Other factors such as advanced age and severity of CHF might also have important roles to play in the pathogenesis of malnutrition. Patients with CHF often suffer from frailty and multiple co-morbidities, such as osteoarthritis, airways disease, renal dysfunction, cognitive impairment, anxiety and depression, which might interact with and/or modify the course of HF and have negative impact on medication adherence, self-care ability and food intake (17). Lack of social support and financial constraints might also limit one's ability to carry out activities of daily living, such as shopping and preparing meals, hence predisposing to malnutrition.

11.6 Study limitations

This is a single-centre study and external validation of our results from other populations is needed. Secondly, I have only studied one of the large number of tools available to screen for malnutrition. Thirdly, this is an observational study, and thus causality cannot be addressed. Additionally, up-titration of anti-HF medications during follow-up for

patients with HeFREF might have led to an improved congestive and nutritional status, and perhaps outcome, in some.

Furthermore, this study is an explorative analysis using a comprehensive prospective data collection undertaken as part of the Hull LifeLab database between 2008 and 2012. The analysis plan was decided post-hoc, and results might have changed overtime, particularly as newer treatments have become available.

The GNRI is derived from serum albumin and the ratio of body weight to ideal body weight. Although it is questionable whether an ideal BMI of 22 kg/m^2 as used in our formula to calculate ideal body weight applies to a UK population, as it might underestimate the prevalence of malnutrition in our population, a recent report from the UK Biobank enrolling > 200,000 UK residents without cardiovascular risk factors supports these findings (209).

Lastly, I have included patients with HeFNEF, for which there is no universally agreed diagnostic definition and some might not accept the definition used in this study which is based on the evidence of signs or symptoms of HF supported by a natriuretic peptide level above the diagnostic level suggested by ESC guidelines (125 ng/L) (5).

11.7 Conclusion

Malnutrition and congestion are both common but are only modestly associated with each other in patients with CHF. The concomitant presence of malnutrition and congestion is strongly associated with a high mortality in patients with CHF; these patients should thus be managed with additional vigilance.

Chapter 12 Effect of Beta-adrenergic Blockade on Weight Changes in Patients with Chronic Heart Failure

12.1 Chapter summary

Background: Weight loss is common in patients with CHF and is associated with adverse outcomes. Activation of the sympathetic nervous system has been implicated in weight loss, wasting and cachexia. However, the effect of sympathetic antagonism on weight change in patients with CHF is not well defined.

Methods: I evaluated changes in body weight, the incidence of cachexia (weight loss > 6%) and significant weight gain (>5%) in unselected ambulatory patients with HeFREF (LVEF <40%) and studied the effect of beta-blockade on weight change.

Results: I studied 1480 patients with HeFREF (median NT-proBNP: 1593 ng/L, median age 72 years): 86% received a beta-blocker, 11% never had a beta-blocker and 3% discontinued beta-blocker between baseline and 1 year.

Patients who did not have or tolerate a beta-blocker were more likely to develop cachexia (23% vs 10%, P<0.001) and less likely to have significant weight gain (22% vs 24%, P<0.001) than patients who had a beta-blocker.

During a median follow up of 1876 (IQR: 993-3052) days, 894 (60%) patients died. Higher BMI at baseline, weight gain and beta-blocker therapy were associated with a better outcome. Patients who had all 3 features: beta-blocker therapy, baseline BMI ≥25 kg/m^2 and significant weight gain had the best outcome (22% mortality at 5 years).

Conclusion: Ambulatory patients with HeFREF who received a beta-blocker were less likely to develop cachexia and more likely to have significant weight gain and better outcome compared to patients who did not receive or tolerate a beta-blocker.

12.2 Introduction

Many chronic conditions are associated with unintentional weight loss, which can be sufficient to be defined as cachexia when weight loss exceeds an arbitrary limit, often taken to be more than 5% in 12 months (66). Weight loss can occur from all body compartments. For patients with CHF, loss of muscle bulk is particularly important because it leads to reduced exercise capacity and worse symptoms (210). The prevalence of cachexia in patients with CHF ranges between 5-15% and is strongly related to an adverse prognosis (5, 168). Treatment trials in patients with cardiac cachexia have been discouraging so far (65, 211).

Activation of the sympathetic nervous system secondary to cardiac dysfunction is implicated in the development of muscle wasting and cachexia (212). Beta-adrenergic blockade reduces muscle catabolism and leads to weight gain both in patients with cardiac and non-cardiac disorders (213, 214). In the Carvedilol Prospective Randomised Cumulative Survival (COPERNICUS) trial, patients randomised to carvedilol were 33% less likely to become cachectic and 37% more likely to have a significant gain in weight (213) than those randomised to placebo. However, the patients in clinical trials are highly selected and may not be representative of the majority of patients with a condition. In this chapter, I will study the effect of beta-blockade on weight change and mortality in a large cohort of unselected, well-characterised patients with CHF to see if the findings from the COPERNICUS trial are generally applicable.

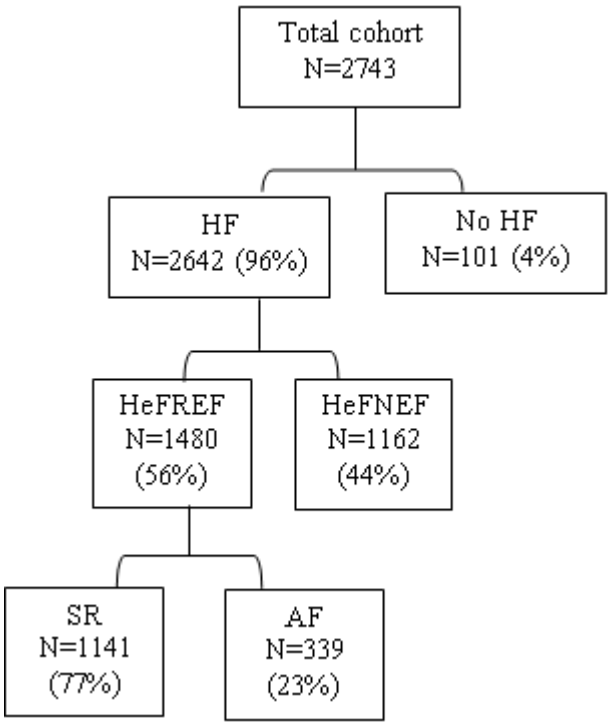
12.3 Methods

12.3.1 Study population

I enrolled consecutive patients from the Hull Lifelab who attended our community HF clinic between 2000 and 2016. All patients had a full medical history, a physical examination and blood tests during baseline visit. A detailed description of the study population and relevant examinations can be found in Chapter 4.

Because a beta-blocker is recommended only for patients with HeFREF, I only included patients with a LVEF <40% (or at least moderate LVSD by visual inspection if LVEF was not measured) (Figure 12.1).

Figure 12.1: Recruitment of patients.



HeFREF = heart failure with reduced ejection fraction, HeFNEF = heart failure with normal ejection fraction, SR = sinus rhythm, AF = atrial fibrillation.

Furthermore, only patients who had weight recorded at baseline and at 1 year visit were included. Patients with weight loss of >6% between baseline and 1 year were defined as having cachexia. I used a higher cut-off than the usual 5% to ensure only patients with significant weight change were included, as weight may fluctuate in patients with CHF as a result of changes in fluid status. Indeed, there is also evidence to suggest that a cut-off of 6% weight loss should be used to define the presence of cachexia in patients with CHF (213). Patients with weight gain of ≥5% from baseline were classified as having significant weight gain (213). For patients who had 3 or more weight measurements recorded between baseline and 1 year visit (N=1361 (92%)), I also determined the variability of body weight by calculating the SD of weight measurements recorded between baseline and 1 year.

All patients were regularly seen in the HF clinic, usually at baseline, after 4 and 12 months, and then yearly, unless an expedited appointment was requested. HF medications were optimised and diuretic dose adjusted to maintain euvolaemia and dry weight. Weight loss with dietary restriction was not routinely advised for overweight or obese patients, although a healthy diet with regular physical exercise was always recommended.

In this study, I classified patients into 4 groups according to their beta-blocker therapy:

1) On beta-blocker therapy at baseline and 1 year;
2) Not on beta-blocker therapy at baseline but on beta-blocker therapy at 1 year;
3) On beta-blocker therapy at baseline but not on beta-blocker therapy at 1 year;
4) Not on beta-blocker therapy at either time points.

As group 3 had very few patients (N=41 (3%)), I excluded this group from further analysis, although patients in group 3 seemed to be sicker than patients in other beta-blocker therapy groups.

I also stratified patients into 3 groups according to their BMI (kg/m^2) (163):

1) Underweight/normal (BMI<25.0);
2) Overweight (BMI = 25.0-29.9);
3) Obese (BMI ≥ 30.0).

12.3.2 End point and follow up

I followed the patients until 9th March 2017 and the primary endpoint was all-cause mortality.

12.3.3 Statistical analysis

Routine statistical analyses have been detailed in Chapter 4.

Firstly, I explored the uptake of beta-blocker therapy in the cohort. Then, I studied the prevalence of cachexia and significant weight gain. Next, I studied the relation between

beta-blocker therapy and weight change. Finally, I explored the relation between beta-blocker therapy, weight change and all-cause mortality using Cox proportional hazards regression. I then constructed Kaplan-Meier curves to present time-to-event data.

12.4 Results

12.4.1 Baseline characteristics

The baseline characteristics of the 1480 CHF patients meeting the inclusion criteria are shown in table 12.1. The median age was 72 years. 75% were male. Median NT-proBNP was 1593 ng/L. 35% had severe symptoms (NYHA III/IV).

Table 12.1: Baseline characteristics of the cohort.

	Total cohort N=1480	Missing
Demographics		
Age (years)	72 (63-78)	0
Sex (male), n (%)	1114 (75)	0
BP systolic (mmHg)	128 (114-145)	2
BP diastolic (mmHg))	77 (67-86)	3
HR (bpm)	73 (63-86)	1
SR, n (%)	1141 (77)	0
Paced rhythm, n (%)	108 (7)	0
Anthropometric measures		
Height (m)	1.70 (1.63-1.76)	0
BL weight (kg)	79.3 (68.0-91.0)	0
BL BMI (kg/m^2)	27.5 (24.4-30.9)	0
1 y weight (kg)	80 (68-92)	0
Weight Δ (BL vs 1 y) (kg)	+0.5 (-2.2 to +3.9)	0
% weight Δ (BL vs 1 y)	+0.5 (-2.8 to +4.9)	0
SD weights (BL to 1y)	2.2 (1.2-3.5)	119
Co-morbidities		
IHD, n (%)	961 (65)	0
Diabetes Mellitus, n (%)	347 (23)	0
HTN, n (%)	462 (31)	0
CVD, n (%)	117 (8)	0
PVD, n (%)	113 (8)	0

Table 12.1 (continued): Baseline characteristics of the cohort.

	Total cohort N=1480	Missing
Clinical examination		
Baseline		
NYHA III/IV, n (%)	514 (35)	0
Lung crackles, n (%)	244 (17)	0
Raised JVP (1-4cm/ earlobe), n (%)	236 (16)	0
Peripheral oedema, n (%)		0
- None-trace	1175 (79)	
- Ankle	206 (14)	
- ≥ Knee	99 (7)	
1 year		
NYHA III/IV, n (%)	339 (23)	0
Lung crackles, n (%)	84 (6)	0
Raised JVP (1-4cm/ earlobe), n (%)	74 (5)	0
Peripheral oedema, n (%)		0
- None-trace	1350 (91)	
- Ankle	88 (6)	
- ≥ Knee	42 (3)	
Blood tests		
Hb (g/dL)	13.6 (12.3-14.7)	0
Urea (mmol/L)	7.1 (5.4-9.5)	0
Creatinine (µmol/L)	105 (88-131)	0
Potassium (mmol/L)	4.4 (4.1-4.7)	2
Sodium (mmol/L)	139 (137-141)	0
BL NT-proBNP (ng/L)	1593 (694-3451)	37
1y NT-proBNP (ng/L)	1081 (425-2357)	59
Δ NT-proBNP (ng/L) (BL vs 1 y)	-100 (-1040 to +70)	79
% Δ NT-proBNP (BL vs 1 y)	-13 (-55 to+12)	79

Table 12.1 (continued): Baseline characteristics of the cohort.

	Total cohort N=1480	Missing
Medications		
Baseline		
ACEi/ ARB, n (%)	1232 (83)	0
BB, n (%)	947 (64)	0
MRA, n (%)	474 (32)	0
Loop diuretics, n (%)	1138 (77)	0
Thiazide diuretics, n (%)	49 (3)	0
Statin, n (%)	793 (54)	0
Digoxin, n (%)	252 (17)	0
1 year		
ACEi/ ARB, n (%)	1361 (92)	0
BB, n (%)	1273 (86)	0
MRA, n (%)	629 (43)	0
Loop diuretics, n (%)	1176 (80)	0
Thiazide diuretics, n (%)	51 (3)	0
Statin, n (%)	891 (60)	0
Digoxin, n (%)	320 (22)	0

NT-ProBNP= N-terminal Pro Brain Natriuretic Peptide, BP= blood pressure, HR = heart rate, BL= baseline, 1y= 1 year, Δ = change, BMI= body mass index, SD= standard deviation, SR= sinus rhythm, IHD= ischaemic heart disease, CVD= cerebral vascular disease, PVD= peripheral vascular disease, JVP= jugular venous pressure, NYHA= New York Heart Association, Hb= haemoglobin, ACEi= angiotensin converting enzyme inhibitor, ARB= angiotensin receptor blocker, MRA= mineralocorticoid receptor antagonist, BB= Beta-blocker.

12.4.2 Beta-blocker therapy

86% of patients received a beta-blocker, 11% never had a beta-blocker and 3% discontinued beta-blocker between baseline and 1 year (Table 12.2). Of the 3 beta-blocker therapy groups I focused on (coloured columns in Table 12.2), patients who did not have beta-blocker therapy at any point were the oldest, most likely to be female, and had the most severe symptoms. They were also the least likely to be on an ACEi/ARB. Patients who did not have beta-blocker therapy at baseline but had beta-blocker therapy at 1 year had the highest baseline NT-proBNP (Table 12.2).

Table 12.2. Baseline characteristics by beta-blocker therapy groups.

	Beta-blocker therapy				P
	BL: √ 1 y: √ N=906 (61%)	BL: × 1 y: √ N=367 (25%)	BL: × 1 y: × N=166 (11%)	BL: √ 1 y: × N=41 (3%)	
Demographics					
Age (years)	70 (61-77)	73 (66-79)	75 (69-81)	72 (66-80)	*
Sex (male), n (%)	704 (78)	265 (72)	112 (68)	33 (81)	0.01
BP systolic (mmHg)	127 (113-144)	132 (117-148)	128 (115-144)	133 (108-151)	0.26
BP diastolic (mmHg)	77 (68-86)	78 (69-89)	77 (68-87)	73 (62-84)	0.01
HR (bpm)	68 (60-80)	81 (71-95)	76 (66-89)	68 (56-83)	*
AF, n (%)	197 (22)	91 (25)	40 (24)	11 (27)	0.59
Paced rhythm, n (%)	72 (8)	18 (5)	15 (9)	3 (7)	0.22
Anthropometric measures					
Height (m)	1.71 (1.65-1.77)	1.69 (1.62-1.75)	1.67 (1.60-1.73)	1.70 (1.61-1.76)	*
BL weight (kg)	81 (70-93)	78 (66-89)	76 (64-88)	76 (66-87)	*
BL BMI (kg/m^2)	27.8 (24.7-31.1)	27.4 (23.7-30.6)	27.1 (24.4-30.5)	26.0 (22.7-30.6)	0.06
1 y weight (kg)	82 (70-94)	79 (67-90)	76 (65-87)	74 (66-88)	*
Weight Δ (BL vs 1 y) (kg)	+0.6 (-2.0 to +3.7)	+0.7 (-2.2 to +4.8)	0 (-3.9 to +3.0)	0 (-2.5 to +3.2)	0.14
% weight Δ (BL vs 1 y)	+0.7 (-2.4 to +4.4)	+1.0 (-2.8 to +6.1)	0 (-4.8 to +4.2)	0 (-3.2 to +4.2)	0.17
SD weights (BL to 1y)	2.1 (1.2-3.4)	2.4 (1.3-4.1)	2.1 (1.3-3.9)	2.0 (1.1-3.5)	0.06

Table 12.2 (continued). Baseline characteristics by beta-blocker therapy groups.

	Beta-blocker therapy				P
	BL: √ 1 y: √ N=906 (61%)	BL: × 1 y: √ N=367 (25%)	BL: × 1 y: × N=166 (11%)	BL: √ 1 y: × N=41 (3%)	
Co-morbidities					
IHD, n (%)	615 (68)	220 (60)	94 (57)	32 (78)	0.001
Diabetes, n (%)	224 (25)	81 (22)	32 (19)	10 (24)	0.42
HTN, n (%)	280 (31)	116 (32)	55 (33)	11 (27)	0.87
CVD, n (%)	72 (8)	26 (7)	17 (10)	2 (5)	0.55
PVD, n (%)	64 (7)	36 (10)	9 (5)	4 (10)	0.23
Clinical examination					
Baseline					
NYHA III/IV, n (%)	276 (30)	126 (34)	87 (52)	25 (61)	*
Crackles, n (%)	106 (12)	83 (23)	45 (27)	10 (24)	*
Raised JVP (1-4cm / earlobe), n (%)	99 (11)	91 (25)	37 (22)	9 (22)	*
Oedema, n (%)					*
- None-trace	777 (86)	256 (70)	115 (69)	27 (66)	
- Ankle	96 (11)	68 (18)	33 (20)	9 (22)	
- ≥ Knee	33 (3)	43 (12)	18 (11)	5 (12)	
1 year					
NYHA III/IV, n (%)	187 (21)	73 (20)	65 (39)	14 (34)	*
Crackles, n (%)	41 (5)	29 (8)	12 (7)	2 (5)	0.09
Raised JVP (1-4 cm/ earlobe), n (%)	41 (5)	19 (5)	12 (7)	2 (5)	0.53
Oedema, n (%)					0.78
- None-trace	835 (92)	328 (89)	149 (90)	38 (93)	
- Ankle	48 (5)	26 (7)	12 (7)	2 (5)	
- ≥ Knee	23 (3)	13 (4)	5 (3)	1 (2)	

Table 12.2 (continued). Baseline characteristics by beta-blocker therapy groups.

	Beta-blocker therapy				P
	BL: √ 1 y: √ N=906 (61%)	BL: × 1 y: √ N=367 (25%)	BL: × 1 y: × N=166 (11%)	BL: √ 1 y: × N=41 (3%)	
Blood tests					
Hb (g/dL)	13.6 (12.4-14.7)	13.6 (12.2-14.7)	13.6 (12.3-14.5)	13.0 (10.5-14.4)	0.10
Urea (mmol/L)	7.1 (5.4-9.6)	6.9 (5.3-9.2)	7.1 (5.1-9.3)	8.0 (6.2-15.4)	0.08
Creatinine (µmol/L)	104 (87-129)	107 (88-128)	105 (90-134)	120 (99-180)	0.005
Potassium (mmol/L)	4.4 (4.2-4.7)	4.3 (4.0-4.6)	4.3 (4.0-4.7)	4.5 (4.1-4.8)	0.009
Sodium (mmol/L)	139 (137-140)	139 (137-141)	139 (136-141)	139 (137-141)	0.52
BL NT-proBNP (ng/L)	1446 (644-3096)	1880 (826-4288)	1642 (663-3769)	2498 (829-6312)	0.001
1y NT-proBNP (ng/L)	1004 (388-2194)	1235 (484-2995)	1083 (461-2221)	1757 (717-3747)	0.007
Δ NT-proBNP (ng/L) (BL vs 1 y)	-102 (-910 to +52)	-146 (-1361 to +146)	-25 (-947 to +110)	-652 (-2862 to +219)	0.44
%Δ NT-proBNP (BL vs 1 y)	-15 (-53 to +8)	-13 (-60 to +22)	-6 (-53 to +16)	-37 (-64 to +25)	0.89
Medications					
Baseline					
ACEi/ ARB, n (%)	809 (89)	274 (75)	115 (69)	34 (83)	*
MRA, n (%)	356 (39)	69 (19)	33 (20)	16 (39)	*
Loop diuretics, n (%)	698 (77)	275 (75)	131 (79)	34 (83)	0.57
Thiazide diuretics, n (%)	24 (3)	11 (3)	13 (8)	1 (2)	0.007
Statin, n (%)	559 (62)	145 (40)	61 (37)	28 (68)	*
Digoxin, n (%)	142 (16)	73 (20)	29 (18)	8 (20)	0.32

Table 12.2 (continued). Baseline characteristics by beta-blocker therapy groups.

	Beta-blocker therapy				P
	BL: √ 1 y: √ N=906 (61%)	BL: × 1 y: √ N=367 (25%)	BL: × 1 y: × N=166 (11%)	BL: √ 1 y: × N=41 (3%)	
Medications					
1 year					
ACEi/ ARB, n (%)	845 (93)	342 (93)	146 (88)	28 (68)	*
MRA, n (%)	428 (47)	120 (33)	64 (39)	17 (42)	*
Loop diuretics, n (%)	701 (77)	302 (82)	139 (84)	34 (83)	0.10
Thiazide diuretics, n (%)	28 (3)	8 (2)	11 (7)	4 (10)	0.007
Statin, n (%)	611 (67)	188 (51)	70 (42)	22 (54)	*
Digoxin, n (%)	175 (19)	79 (22)	55 (33)	11 (27)	0.001

*P<0.001.

NT-ProBNP= N-terminal Pro Brain Natriuretic Peptide, BP= blood pressure, HR = heart rate, BL= baseline, 1y= 1 year, Δ = change, BMI= body mass index, SD= standard deviation, AF= atrial fibrillation, IHD= ischaemic heart disease, CVD= cerebral vascular disease, PVD= peripheral vascular disease, HTN= hypertension, JVP= jugular venous pressure, NYHA= New York Heart Association, Hb= haemoglobin, ACEi= angiotensin converting enzyme inhibitor, ARB= angiotensin receptor blocker, MRA= mineralocorticoid receptor antagonist.

12.4.3 Cachexia and significant weight gain

Cachexia occurred in 13% (N=185) and significant weight gain occurred in 24% (N=363) of patients (Table 12.3). Compared to those with significant weight gain or stable weight, those who developed cachexia were older, had higher BMI, worse symptoms, higher baseline NT-proBNP, worse renal function, were less likely to be on an ACEi/ARB or an MRA at baseline and had a smaller fall in NT-proBNP at 1 year (Table 12.3).

Table 12.3: Baseline characteristics by weight change categories.

	Δ Weight (BL vs 1 y)			P
	Loss >6% N=185 (13%)	Loss ≤ 6% to Gain ≤ 5% N=932 (63%)	Gain >5% N=363 (24%)	
Demographics				
Age (years)	73 (66-78)	72 (64-78)	70 (62-77)	0.007
Sex (male), n (%)	125 (68)	730 (78)	259 (71)	0.001
BP systolic (mmHg)	126 (110-142)	130 (116-147)	125 (111-141)	0.003
BP diastolic (mmHg)	75 (67-84)	77 (68-86)	77 (65-87)	0.32
HR (bpm)	77 (66-92)	71 (61-84)	76 (66-89)	*
AF, n (%)	52 (28)	201 (22)	86 (24)	0.14
Paced rhythm, n (%)	16 (9)	73 (8)	19 (5)	0.20
Anthropometric measures				
Height (m)	1.68 (1.61-1.76)	1.70 (1.64-1.76)	1.69 (1.62-1.75)	0.01
BL weight (kg)	80 (68-95)	81 (70-91)	75 (62-87)	*
BL BMI (kg/m^2)	28.6 (24.8-32.7)	27.9 (24.9-31.1)	25.9 (22.9-29.2)	*
1 y weight (kg)	71 (61-84)	81 (70-92)	83 (69-96)	*
SD weights (BL to 1y)	4.2 (3.3-6.3)	1.5 (0.9-2.1)	3.8 (2.8-5.3)	*
Co-morbidities				
IHD, n (%)	115 (62)	631 (68)	215 (59)	0.01
Diabetes, n (%)	55 (30)	201 (22)	91 (25)	0.04
HTN, n (%)	57 (31)	296 (32)	109 (30)	0.83
CVD, n (%)	15 (8)	74 (8)	28 (8)	0.99
PVD, n (%)	15 (8)	71 (8)	27 (7)	0.96

Table 12.3 (continued): Baseline characteristics by weight change categories.

	Δ Weight (BL vs 1 y)			P
	Loss >6% N=185 (13%)	Loss ≤ 6% to Gain ≤ 5% N=932 (63%)	Gain >5% N=363 (24%)	
Clinical examination				
Baseline				
NYHA III/IV, n (%)	85 (46)	312 (33)	117 (32)	0.02
Crackles, n (%)	47 (25)	140 (15)	57 (16)	0.002
Raised JVP (1-4cm / earlobe), n (%)	44 (24)	133 (14)	59 (16)	0.005
Oedema, n (%)				*
- None-trace	121 (66)	755 (81)	299 (82)	
- Ankle	32 (17)	125 (13)	49 (14)	
- ≥ Knee	32 (17)	52 (6)	26 (4)	
1 year				
NYHA III/IV, n (%)	59 (32)	215 (23)	65 (18)	0.002
Crackles, n (%)	10 (5)	57 (6)	17 (5)	0.60
Raised JVP (1-4 cm/ earlobe), n (%)	13 (7)	41 (4)	20 (6)	0.29
Oedema, n (%)				0.69
- None-trace	165 (89)	853 (91)	332 (91)	
- Ankle	23 (7)	56 (6)	20 (6)	
- ≥ Knee	8 (4)	23 (3)	11 (3)	
Blood tests				
Hb (g/dL)	13.2 (12.0-14.4)	13.6 (12.4-14.7)	13.7 (12.3-14.8)	0.18
Urea (mmol/L)	7.9 (5.6-10.7)	6.8 (5.3-9.0)	7.5 (5.4-10.0)	*
Creatinine (µmol/L)	114 (90-138)	104 (88-128)	104 (85-134)	0.10
Potassium (mmol/L)	4.3 (4.1-4.7)	4.4 (4.1-4.7)	4.3 (4.0-4.7)	0.50
Sodium (mmol/L)	139 (137-141)	139 (137-141)	138 (136-140)	0.06

Table 12.3 (continued): Baseline characteristics by weight change categories.

	Δ Weight (BL vs 1 y)			P
	Loss >6% N=185 (13%)	Loss ≤ 6% to Gain ≤ 5% N=932 (63%)	Gain >5% N=363 (24%)	
Blood tests				
BL NT-proBNP (ng/L)	2090 (929-5531)	1463 (645-3131)	1784 (724-3769)	*
1y NT-proBNP (ng/L)	1801 (660-4431)	1040 (421-2206)	896 (346-2254)	*
Δ NT-proBNP (ng/L) (BL vs 1 y)	0 (-1011 to +219)	-63 (-913 to +106)	-380 (-1543 to 0)	*
%Δ NT-proBNP (BL vs 1 y)	0 (-48 to +17)	-10 (-48 to +16)	-33 (-70 to 0)	*
Medications				
Baseline				
ACEi/ ARB, n (%)	144 (78)	779 (84)	309 (85)	0.09
MRA, n (%)	53 (29)	285 (31)	136 (38)	0.03
Loop diuretics, n (%)	152 (82)	682 (73)	304 (84)	*
Thiazide diuretics, n (%)	8 (4)	29 (3)	12 (3)	0.70
Statin, n (%)	85 (46)	541 (58)	167 (46)	*
Digoxin, n (%)	37 (20)	130 (14)	85 (23)	*
1 year				
ACEi/ ARB, n (%)	154 (83)	862 (93)	345 (95)	*
MRA, n (%)	81 (44)	398 (43)	150 (41)	0.84
Loop diuretics, n (%)	160 (87)	719 (77)	297 (82)	0.007
Thiazide diuretics, n (%)	13 (7)	27 (3)	11 (3)	0.02
Statin, n (%)	96 (52)	597 (64)	198 (55)	*
Digoxin, n (%)	65 (35)	175 (19)	80 (22)	*

Table 12.3 (continued): Baseline characteristics by weight change categories.

	Δ Weight (BL vs 1 y)			P
	Loss >6% N=185 (13%)	Loss ≤ 6% to Gain ≤ 5% N=932 (63%)	Gain >5% N=363 (24%)	
Medications				
Beta-blocker groups				*
BL & 1y: √	93 (50)	601 (64)	212 (58)	
BL: × 1y: √	49 (26)	211 (23)	107 (30)	
BL: √ 1y: ×	5 (3)	29 (3)	7 (2)	
BL & 1y: ×	38 (21)	91 (10)	37 (10)	

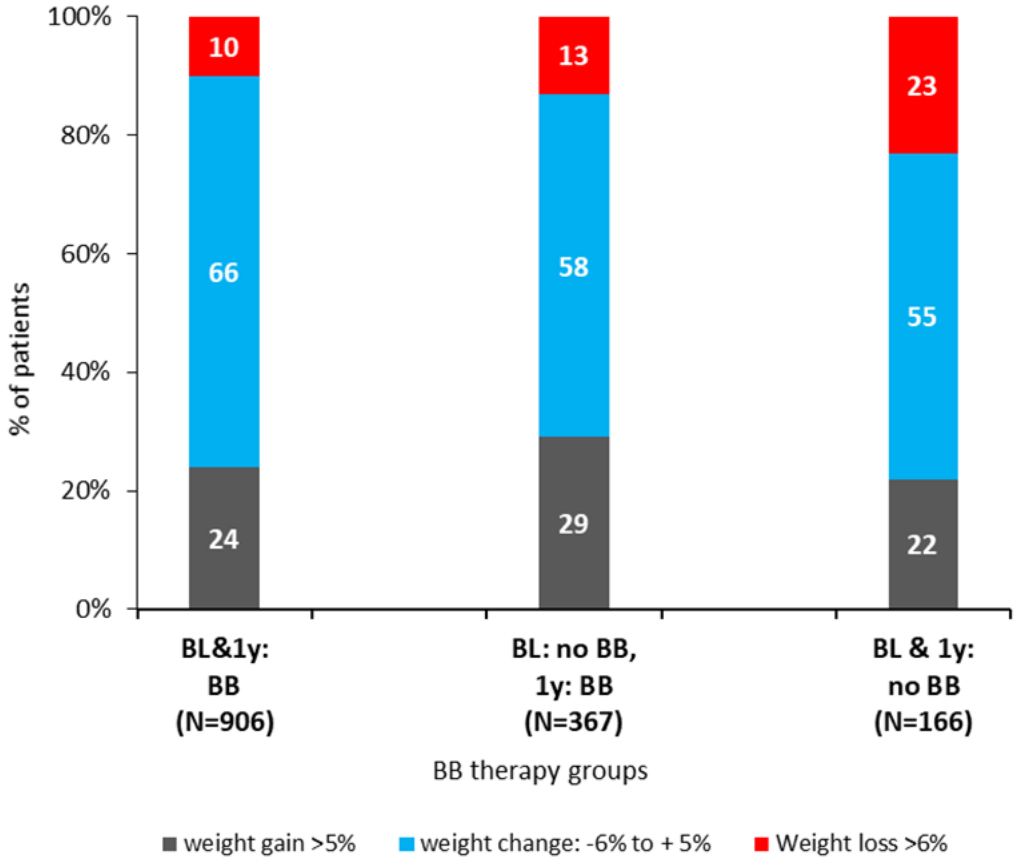
*P<0.001.

NT-proBNP= N-terminal Pro Brain Natriuretic Peptide, BP= blood pressure, HR = heart rate, BL= baseline, 1y= 1 year, Δ = change, BMI= body mass index, SD= standard deviation, AF= atrial fibrillation, IHD= ischaemic heart disease, CVD= cerebral vascular disease, PVD= peripheral vascular disease, HTN= hypertension, JVP= jugular venous pressure, NYHA= New York Heart Association, Hb= haemoglobin, ACEi= angiotensin converting enzyme inhibitor, ARB= angiotensin receptor blocker, MRA= mineralocorticoid receptor antagonist.

12.4.4 Weight change and beta-blocker therapy

The incidence of cachexia was higher in patients who did not have beta-blocker therapy than in patients who had beta-blocker therapy at baseline and 1 year (P<0.001) (Figure 12.2). The incidence of significant weight gain was higher in patients who had beta-blocker therapy either at baseline or initiated between baseline and 1 year than in patients who did not have beta-blocker therapy (P<0.001) (Figure 12.2).

Figure 12.2: Degree of weight change by beta-blocker therapy groups. (The numbers within the bars represent the % of patients within each weight change category)

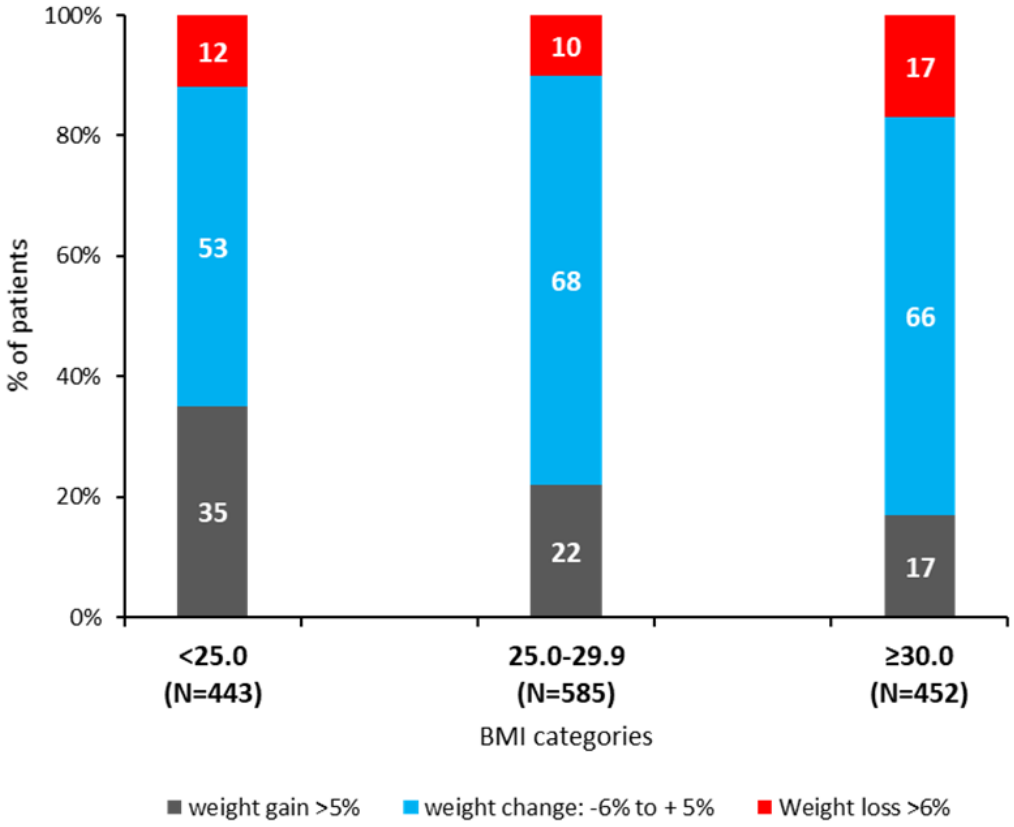


P<0.001. BB= beta-blocker, BL = baseline, 1y = 1 year.

12.4.5 Weight change and baseline BMI

The incidence of cachexia was higher in patients who were obese (BMI ≥ 30 kg/m^2) than in patients who were overweight (BMI = 25.0-29.9 kg/m^2) or normal/underweight (BMI <25 kg/m^2) (P<0.001) (Figure 12.3). The incidence of significant weight gain was lower in obese patients than in patients who were overweight or normal/ underweight (P<0.001) (Figure 12.3).

Figure 12.3: Degree of weight change by baseline BMI groups. (The numbers within the bars represent the % of patients within each weight change category)



P<0.001. BMI = body mass index.

12.4.6 Variability in weight

Amongst the 1361 patients (92%) with ≥3 weight measurements during the first year of follow up, the median SD in weight was 2.2 (IQR: 1.2-3.5) kg. There was no difference in the variability of weight amongst patients of different beta-blocker therapy groups (Table 12.2) Patients with BMI ≥ 30 kg/m^2 had the greatest variability in body weight compared to patients in other BMI categories (Table 12.4).

Table 12.4: Variability in weight by BMI categories.

BMI categories (kg/m^2)	Variability in weight (SD)		P
	Median	IQR	
<25	2.1	1.1-3.5	<0.001
25.0-29.9	1.9	1.2-3.2	
≥ 30	2.5	1.5-4.1	

BMI= body mass index, SD= standard deviation, IQR= interquartile range

12.4.7 Prognostic importance of weight change, baseline BMI and beta-blocker therapy

Patients were followed from the end of the first year onward. During a median subsequent follow up of 1876 (IQR: 993-3052) days, 894 (60%) patients died. Univariable and multivariable predictors of mortality are shown in Table 12.5. In univariable analysis, increasing BMI, significant weight gain and beta-blocker therapy were associated with a better outcome. In multivariable analysis, the development of cachexia and the absence of beta-blocker therapy were independently associated with increasing all-cause mortality.

Table 12.5: Univariable and multivariable analyses of factors predicting all-cause mortality.

Worse outcome per unitary increase	Univariable			Multivariable		
	HR (95%CI)	χ^2	P	HR (95%CI)	χ^2	P
Age (years)	1.06 (1.05-1.07)	226.1	*	1.04 (1.03-1.05)	71.7	*
BP diastolic (mmHg)	0.99 (0.98-0.99)	36.6	*	0.99 (0.99-1.00)	8.1	0.004
AF (Y vs N)	1.33 (1.15-1.55)	13.9	*			
Paced rhythm (Y vs N)	1.30 (1.02-1.68)	4.3	0.04			
BL BMI (kg/m^2)	0.97 (0.96-0.99)	18.3	*			
NYHA (III/IV vs I/II)	1.59 (1.39-1.81)	44.7	*			
Oedema (> vs < ankle)	1.55 (1.21-1.98)	12.2	*			

Table 12.5 (continued): Univariable and multivariable analyses of factors predicting all-cause mortality.

Worse outcome per unitary increase	Univariable			Multivariable		
	HR (95%CI)	χ^2	P	HR (95%CI)	χ^2	P
Weight Δ						
Gain >5%	Referent			Referent		
-6 to +5%	1.06 (0.90-1.24)	0.5	0.49	1.15 (0.96-1.38)	2.2	0.14
Loss <6%	1.62 (1.30-2.02)	18.7	*	1.42 (1.10-1.84)	7.2	0.007
Diabetes (Y vs N)	1.22 (1.05-1.43)	6.6	0.01	1.23 (1.03-1.48)	5.3	0.02
IHD (Y vs N)	1.27 (1.10-1.46)	10.5	0.001	1.36 (1.14-1.62)	12.1	*
HTN (Y vs N)	1.23 (1.07-1.41)	8.6	0.003	1.27 (1.08-1.49)	8.3	0.004
CVD (Y vs N)	1.37 (1.10-1.71)	8.1	0.004			
PVD (Y vs N)	1.65 (1.33-2.06)	20.5	*	1.59 (1.24-2.04)	13.1	*
Log [NT-proBNP]	2.54 (2.21-2.91)	178.6	*	1.89 (1.58-2.25)	48.4	*
Hb (g/dL)	0.86 (0.83-0.89)	54.8	*			
Urea (mmol/L)	1.08 (1.07-1.09)	155.6	*	1.04 (1.02-1.05)	19.4	*
Creatinine (µmol/L)	1.01 (1.00-1.01)	122.7	*			
Sodium (mmol/L)	0.97 (0.95-0.99)	6.6	0.01			
Digoxin (Y vs N)	1.23 (1.04 -1.47)	5.7	0.02			
ACEi/ ARB						
BL & 1 y: √	Referent					
BL: × 1y: √	1.13 (0.94-1.36)	1.6	0.21			
BL: √ 1y: ×	1.62 (1.23-2.14)	11.6	0.001			
BL & 1 y: ×	1.33 (0.93-1.91)	2.4	0.12			
Beta-blocker						
BL & 1 y: √	Referent			Referent		
BL: × 1y: √	1.38 (1.18-1.60)	17.1	*	1.15 (0.97-1.37)	2.4	0.12
BL & 1 y: ×	1.87 (1.54-2.28)	40.3	*	1.47 (1.17-1.85)	10.7	0.001

*P<0.001.

BP=blood pressure, AF= atrial fibrillation, BMI= body mass index, NYHA= New York Heart Association, Δ= change, IHD= ischaemic heart disease, HTN= hypertension, CVD= cerebrovascular disease, PVD= peripheral vascular disease, Hb= haemoglobin, NT-proBNP= N-terminal pro B-type natriuretic peptide, ACEi= angiotensin converting enzyme inhibitor, ARB= angiotensin receptor blocker, HR = hazard ratio, CI= confidence interval, χ2= chi-square, Y= yes, N=No.

Kaplan-Meier curves for the relationship between weight change, beta-blocker therapy and outcome are shown in Figures 12.4 and 12.5. Compared to patients with significant weight gain, those who developed cachexia had a 60% higher risk of all-cause death (Figure 12.4). Compared to patients who had beta-blocker therapy at baseline and 1 year, those who did not have beta-blocker therapy at both time points had a 90% higher risk of all-cause death (Figure 12.5).

Figure 12.4: Kaplan Meier curves illustrating the relation between weight change categories and all-cause mortality.

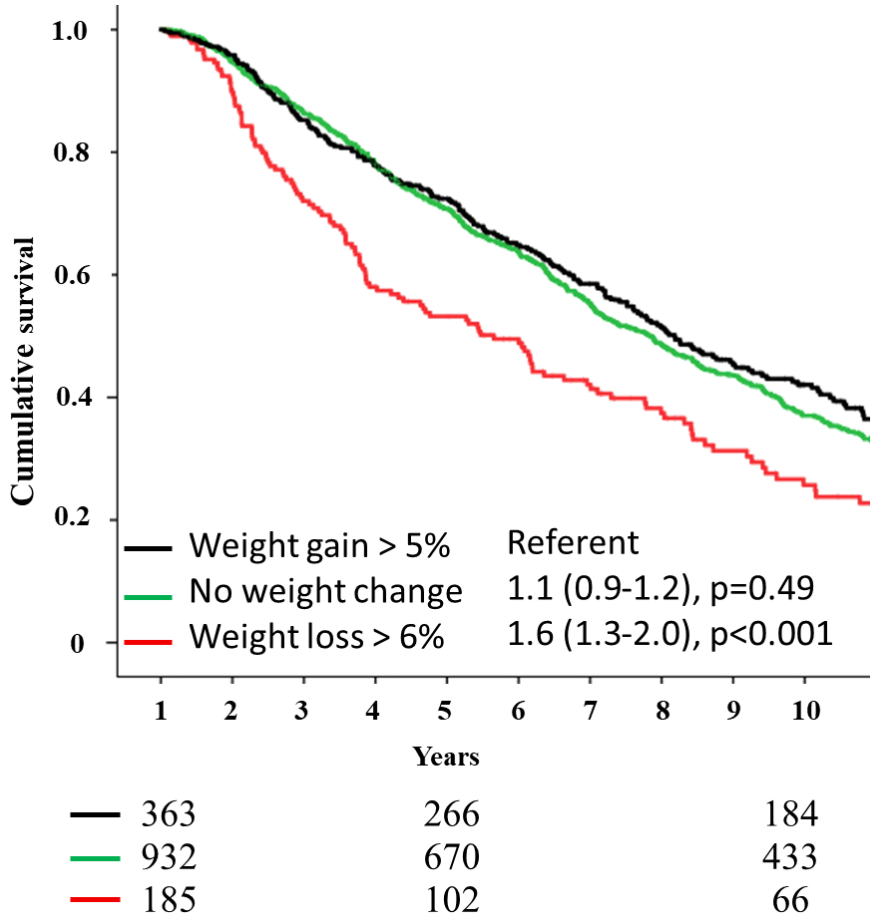
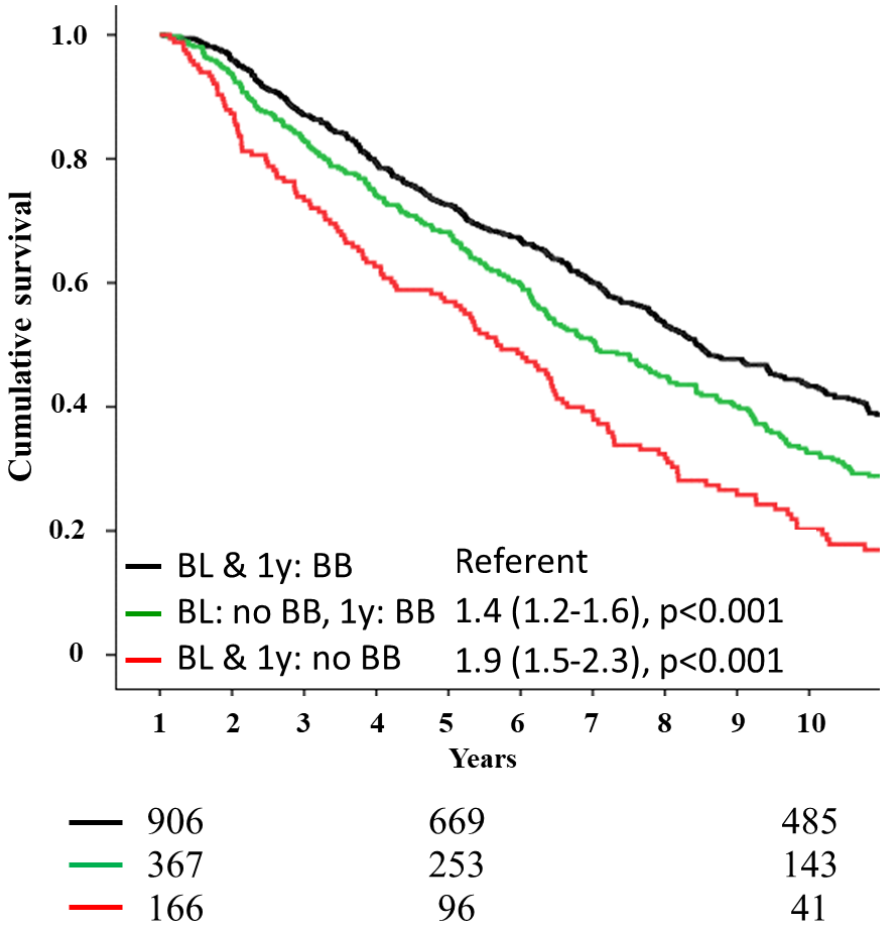


Figure 12.5: Kaplan Meier curves illustrating the relation between beta-blocker therapy groups and all-cause mortality.



BB= beta-blocker, BL= baseline, 1y= 1 year.

Tables 12.6a-b show the 1-year and 5-year mortality rates for patients divided by category of weight change, BMI and beta-blocker therapy. Patients with CHF who had the following 3 features: beta-blocker therapy both at baseline and 1 year, baseline BMI ≥25 kg/m^2 and significant weight gain had the best outcome, while patients who did not have any of the above 3 features (i.e.no beta-blocker therapy at either time point; baseline BMI<25 kg/m^2 and cachexia) had the worst outcome (1-year mortality: 2% vs 18%, 5-year mortality: 22% vs 73%) (Tables 12.6a-b).

Table 12.6a: 1-year mortality by categories of weight change, BMI and beta-blocker therapy.

		Weight change & BMI categories					
		BMI ≥ 25			BMI < 25		
		Weight↑ >5%	Weight Δ -6% to +5%	Weight↓ >6%	Weight↑ >5%	Weight Δ -6% to +5%	Weight↓ >6%
Beta-blocker groups	BL: √ 1y: √	2% (N=132)	3% (N=455)	8% (N=67)	5% (N=80)	6% (N=146)	15% (N=26)
	BL: × 1y: √	4% (N=55)	6% (N=151)	8% (N=36)	6% (N=52)	8% (N=60)	15% (N=13)
	BL: × 1y: ×	5% (N=19)	13% (N=70)	11% (N=27)	17% (N=18)	14% (N=21)	18% (N=11)

Table 12.6b: 5-year mortality by categories of weight change, BMI and beta-blocker therapy.

		Weight change & BMI categories					
		BMI ≥ 25			BMI < 25		
		Weight↑ >5%	Weight Δ -6% to +5%	Weight↓ >6%	Weight↑ >5%	Weight Δ -6% to +5%	Weight↓ >6%
Beta-blocker groups	BL: √ 1y: √	22% (N=132)	28% (N=455)	42% (N=67)	31% (N=80)	39% (N=146)	46% (N=26)
	BL: × 1y: √	40% (N=55)	34% (N=151)	42% (N=36)	42% (N=52)	42% (N=60)	46% (N=13)
	BL: × 1y: ×	37% (N=19)	50% (N=70)	56% (N=27)	56% (N=18)	38% (N=21)	73% (N=11)

BL= baseline, 1 y = 1 year.

12.5 Discussion

The main finding of this study is that amongst patients with HeFREF, those who were not receiving or were unable to take a beta-blocker were more likely to develop cachexia and less likely to have significant weight gain than patients who received beta-blocker therapy. Significant weight gain and beta-blocker therapy were independently associated with improved survival. Our results are similar to those from the COPERNICUS trial, which studied 2289 patients with HF and LVEF <25%. Compared to patients randomised to placebo, those who received carvedilol were 33% less likely to become cachectic (weight loss >6%) and 37% more likely to have a significant gain in weight (≥5%): these changes were associated with a better outcome (213).

It is difficult to dissect the exact causal explanation for these findings. The beneficial effects of beta-adrenergic blockade on cardiac cachexia might be related to the role of sympathetic activation on the development of cardiac cachexia (215). Patients with CHF have marked sympathetic activation; in particular cachectic patients have a higher level of circulating noradrenaline than non-cachectic patients with HF (196).

Sympathetic activation might contribute to cachexia by increasing total body energy expenditure (216) and directly exerting a myotoxic effect on skeletal muscles (217). It also increases the secretion of leptin, stimulates the release of pro-inflammatory cytokines and promotes the development of insulin resistance, all of which can lead to wasting of muscle and adipose cells (65, 91).

Beta-blockade reduces total body resting energy expenditure and prevents catecholamine-induced myotoxicity (218). Beta-blockade might also prevent weight loss by improving fatigue and exercise tolerance (219), perhaps in association with improved appetite. Inhibition of the renin-angiotensin system in patients with CHF by ACEi and ARB also reduces the likelihood of weight loss (95, 99), suggesting that there is a strong relation between neurohormonal activation and weight loss.

Although obesity is a risk factor for developing HF, once HF develops, a higher BMI is associated with better survival, a phenomenon sometimes called the “obesity paradox” (105). Current guidelines do not recommend weight loss in patients with CHF and BMI<35 kg/m^2 (5). This study shows that incident cachexia is more common in obese

patients than normal weight patients. It is important to acknowledge that weight loss in obese patients carries a poor prognosis, even though weight loss might result in a BMI still within the normal range (102). Patients who are a normal weight/BMI and who develop HF have less weight to lose than those who are obese. However, the prognosis seems to be related to proportional loss of weight, and so their prognosis is better than in obese patients who lose weight. Weight loss in an obese patient should therefore trigger the same if not more concern as weight loss in a patient with normal weight.

Weight loss is a poor prognostic sign and should alert the physician that the patient is deteriorating. Beta-blockers attenuate weight loss, emphasising the importance of their use in all patients with HeFREF as soon as possible after the diagnosis is made.

12.6 Study limitations

Firstly, the definition of cachexia is arbitrary and might not be appropriate in all patients with CHF. Changes in weight following treatment, including beta-blockers, ACEi and diuretics, might be related to changes in fluid status rather than loss of muscle or fat mass. However, it would be highly unlikely that many ambulatory patients with CHF have substantial (>5% of body weight) fluid accumulation.

Secondly, patients were enrolled between 2000 and 2016, and clinical practice has substantially changed over this period. I did not look at changes in the incidence of cachexia over time in this study. It is possible that the prevalence of cachexia is increasing as patients age and are at lower risk of sudden death compared to around 20 years ago (220).

Thirdly, I cannot ascertain whether weight loss was intentional or unintentional and I did not collect information on whether weight loss occurred in the presence of concomitant co-morbidities, such as cancer, which would have contributed to incident cachexia, and worse outcome, at least in some.

Fourthly, I only analysed weight change during baseline and 1 year follow-up, and thus those who died within a year, or did not attend 1-year follow-up visit, were not included in the analysis. Moreover, weight change from 1 year to time of event was not studied.

Fifthly, the effect of beta-blockade on cachexia might be confounded by other factors, such as changes in other anti-HF medications or the use of cardiac resynchronisation therapy, both of which prevent weight loss in patients (95).

In addition, I also found that patients who did not receive beta-blockers at any time were the oldest and sickest; they also had the worst prognosis. It would be interesting to know whether survival in this group is related to the duration since HF diagnosis. I included patients from their first visit to the HF service and data from before presentation were not available. However, I have no reason to suspect that this particular group had HF for longer than other patients.

Finally, this is a single-centre observational study conducted in the UK; external validation of our results from other populations is needed.

12.7 Conclusion

Around 13% of ambulatory patients with HeFREF develop cachexia during one year follow up. Compared to patients treated with beta-blockers, those who were not were at higher risk of developing cachexia and had worse survival. These findings support the role of sympathetic antagonism in the prevention of cachexia.

Chapter 13 Conclusion: Key Findings, Clinical Implications and Future Research

13.1 Key findings

(1) Frailty and malnutrition are common in patients with HF.

The prevalence of frailty and malnutrition in patients with HF is much higher than those at risk of developing HF but have no overt signs or symptoms of HF. The prevalence of frailty and malnutrition in patients admitted with AHF with LVSD is around 50%. The prevalence of frailty in patients with CHF is 30-53%, depending on the tool used. The prevalence of malnutrition in patients with CHF is highly variable, depending on the tool used (any degree of malnutrition: 6-60%; moderate to severe malnutrition: 3-9%).

The prevalence of frailty is higher in patients with HeFNEF compared to those with HeFREF and in patients with AF compared to those in SR. There is no difference in the prevalence of malnutrition in patients with different HF phenotypes or cardiac rhythm.

(2) HF patients who are frail and malnourished have different characteristics compared to those who are not.

Frail and malnourished patients are older, have worse HF symptoms (higher NYHA class), higher NT-proBNP, lower BMI, worse renal function and anaemia. They are also more likely to suffer from co-morbidities such as dementia, COPD, depression, recurrent falls and urinary incontinence. They are more likely to be on diuretics but less likely to be on other HF medications such as ACEi, beta-blockers and MRA.

(3) Frailty and malnutrition predict worse morbidity and mortality in patients with HF.

All frailty and malnutrition tools are independent predictors of increased mortality in patients with HF independent of age, co-morbidities, Hb, renal function, NYHA class and NT-proBNP.

(4) Frailty and malnutrition have a dose-dependent effect on morbidity and mortality in patients with HF.

In patients with CHF, 1-year mortality rate for severely frail, pre-frail and non-frail patients are 33-74%, 2-13% and 1-2% respectively. 1-year mortality rate for patients with the worst and the best nutritional status are 33-47% and 2-4% respectively. In patients admitted with HF, 1-year mortality is 1% for those who were neither frail nor malnourished; 15% for those who were either frail or malnourished; and 65% for those who were both frail and malnourished.

(5) Simple frailty screening tools such as the clinical frailty scale (CFS) and 5-meter walk tests (5MWT) provide comparable prognostic information to longer assessment tools. Serum albumin provides comparable prognostic information to simple or multi-dimensional malnutrition tools.

(6) Malnutrition is possibly related to historical congestion.

There is a modest association between malnutrition and current congestion status in patients with CHF. Interestingly, patients with previous admissions for HF are more likely to be malnourished and have evidence of right heart dysfunction. This implies a potential link between malnutrition and historical congestion.

(7) Sympathetic antagonism might have a role in preventing the development of cachexia. Around 13% of patients with HeFREF develop cachexia at 1 year. Those who were not treated with beta-blockers are at a higher risk of developing cachexia and have worse outcome compared to those who received beta-blockers.

13.2 Clinical implications

Traditional prognostic models for HF are mostly constructed using clinical variables. Other important non-clinical variables such as frailty and malnutrition, functional and social status, are often not included. This thesis provided strong evidence regarding the clinical and prognostic role of frailty and malnutrition in patients with HF. I believe that frailty and malnutrition should be routinely evaluated in clinical practice to identify

patients at risk of poor outcome. I also believe that incorporating frailty and malnutrition into future prognostic models of HF will be beneficial. Simple tools such as CFS, 5MWT and measuring serum albumin levels, are quick and easy to perform and provide comparable prognostic information to longer assessment tools. Simple tools may be useful for the rapid evaluation of frailty and malnutrition in HF patients in busy clinical settings. Identification of 'pre-frailty' or 'mild degree of malnutrition' at an early stage might allow introduction of interventions such as exercise training programmes, medication review and nutritional optimisation, which may delay the development of frailty and malnutrition. Identification of frailty, especially in patients with moderate or severe frailty, is helpful on decision-making regarding potential ceilings of care and palliative treatment.

13.3 Future research

Future research should target interventions for frailty and malnutrition in patients with HF.

Study 1: Exercise training

Background: Exercise-based cardiac rehabilitation in stable HF patients with LVSD is safe and effective in improving symptoms, exercise capacity and QoL, and reducing hospitalisations (221-223). The role of exercise therapy in patients with HeFNEF is less clear (223). Exercise training in frail older adults not only enhances physical functioning, it also improves balance, body composition, nutritional status as well as psychological and neurological function (224). So far, the role of exercise therapy in managing frailty in HF patients is not established.

Aim: To investigate the effect of exercise training on functional capacity, frailty status, QoL, morbidity and mortality in HF patients who are frail.

Design: RCT

Methods: Patients attending our community HF clinic will be screened for frailty using the CFS. Patients with mild to moderate frailty would be eligible for randomisation. The

Participants will be randomised to either the intervention (standard care + 12-week individualised exercise training programme) or control (standard care) group. Participants in the intervention arm will be taught a set of simple, graded strength and resistance home-based exercise which lasts 15-30 minutes by a professional sports science researcher. Participants will be encouraged to repeat the set of exercise on a daily basis. To ensure compliance, participants will be reviewed in person on a weekly basis until completion of the exercise programme. Functional assessments, frailty status and QoL questionnaire will be completed during each visit. Hospitalisation and mortality data will be obtained after completion of the exercise programme and at 6 month follow up.

Study 2: Co-enzyme Q10 (CoQ10)

Background:

Advanced age and frailty are associated with oxidative imbalance (225). Increased oxidative stress contributes to progression of HF by disrupting myocyte metabolism (226). CoQ10 is a co-enzyme for mitochondrial enzymes and a cell membrane stabiliser (116). Decreased CoQ10 is associated with a wide range of degenerative diseases including HF (116, 227). CoQ10 supplementation has antioxidant properties and might improve endothelial function (227). To date, there is no convincing evidence to support or refute the use of CoQ10 for management of HF (116, 227).

Q-symbio is a large, double-blinded, multi-centre RCT which evaluated the effect of CoQ10 supplementation in 420 patients with HF. The study showed that CoQ10 supplementation is safe; improves HF symptoms and reduces major cardiovascular events (228). However, the trial had significant recruitment issues and was not completed according to the original enrolment plan.

Aims: To evaluate the effect of CoQ10 on functional outcomes, frailty status, QoL, morbidity and mortality in HF patients who are frail.

Design: Randomised, double-blinded, placebo-controlled crossover study (Table 13.1)

Methods: Patients attending our community HF clinic will be screened for frailty using the CFS. Patients with mild to moderate frailty would be eligible for randomisation.

Participants will be randomised to either the intervention (standard care + CoQ10 supplementation) or control (standard care + placebo) group. Participants in the intervention arm will be given CoQ10 supplementation as a solubilised preparation to enhance absorption (116, 227), at a dosage of 100mg 3 times a day according to the Q-symbio trial (228). CoQ10 supplementation will be given for 3 months as current data suggest that most patients experience possible benefits within 3 months of treatment (227). Participants in the intervention group will then then cross over to the control group and vice versa with a wash out period. As the elimination half-life of CoQ10 is approximately 33 hours (229), a washout period of 1 week (>5 times the half-life of CoQ10) will be used. Participants will be reviewed on a monthly basis to ensure compliance. During follow up, functional assessments, frailty status and QoL questionnaire will be completed. Hospitalisation and mortality data will be obtained after the 25-week study-period and at 6 month follow up.

Table 13.1: CoQ10 intervention study design.

		Time period		
		Weeks 1-12		Weeks 13-25
Intervention	A	CoQ10 100mg 3 times a day	Washout period (1 week) + Cross over	Placebo
	B	Placebo		CoQ10 100mg 3 times a day

Other potential nutritional supplementation intervention include the following:

1) Vitamin D

   A systematic review of 8 RCTs with >70,000 elderly patients with vitamin D deficiency, showed that vitamin D supplementation reduced mortality by 7% (160). However, another systematic review of 81 RCTs showed that vitamin D supplementation had no effect on fractures or falls (230). The role of vitamin D supplementation in HF patients who are frail is unclear.

2) Testosterone

Testosterone deficiency is common in patients with HF (231). It is associated with muscle wasting, reduced exercise capacity and increased mortality (231). Testosterone therapy in patients with HF is associated with improvement in 6-minute walk test and peak oxygen consumption, with no significant cardiovascular adverse events (232). The role of testosterone therapy in HF patients who are frail is unclear.

3) Protein/ energy supplementation

A systematic review of 62 RCTs involving 10,187 participants concluded that oral protein and energy supplementation promoted weight gain in older adults, but its effect on function, morbidity and mortality needs further clarification (233). The role of protein or energy supplementation in HF patients who are frail is unclear.

Study 3: Multi-factorial, multi-disciplinary intervention (Please see list of grant application)

Background: An Australian RCT involving 241 participants showed that a 12-month multi-factorial, multi-disciplinary intervention improved mobility and prevented deterioration in frailty status in older adults (234).

Aims: To evaluate the effect of a multi-factorial, multi-disciplinary intervention on functional outcomes, frailty status, QoL, morbidity and mortality in HF patients who are frail.

Design: RCT

Methods: Patients attending our community HF clinic will be screened for frailty using the CFS. Patients with mild to moderate frailty would be eligible for randomisation. Participants will be randomised to either the intervention and standard care or standard care alone. The intervention will be a 6-month comprehensive geriatric assessment based programme, individually tailored to each participant according to their frailty status. The programme includes reviews by a multi-disciplinary team including dieticians, psychiatrists, physiotherapists and physicians with appropriate interventions including home-delivered meals, nutritional supplementation, home exercise programmes,

medication review, remote symptom monitoring and chronic disease management. The effect of the intervention on frailty status, functional outcomes, QoL, morbidity and mortality will be studied.

Study 4: The association between non-adherence to HF medications and frailty in patients with HF.

Background: An observation that I made whilst performing frailty and malnutrition assessments in patients with HF is that polypharmacy and non-adherence to medications for HF are especially common in those who are frail or malnourished.

Aims: To study the association between frailty and non-adherence to HF medications and its subsequent impact on hospitalisation and mortality in patients with CHF.

Design: Prospective cohort study

Methods: This project will be a collaboration between the Department of Academic Cardiology, Castle Hill Hospital, Hull and the Department of Chemical Pathology and Metabolic Diseases, University Hospitals of Leicester. Leicester has developed a unique biochemical technique using liquid chromatography-tandem mass spectrometry to detect non-adherence to 60 common cardiovascular medications in a spot blood sample. Stored blood samples from the cohort of patients with HF studied in Chapter 7-10 will be analysed using tandem mass spectrometry. The prevalence of non-adherence to HF medications in frail compared to non-frail patients and its impact on morbidity and mortality will be studied.

Study 5: The biochemical diagnosis of non-adherence in CHF: its prevalence, cost-effectiveness and association with adverse outcome.

Background: Non-adherence contributes to treatment failure in CHF, leading to worsening symptoms, frequent hospitalisations and death (235). The prevalence of non-adherence has been estimated to range from 4-30% in different cohorts of patients with

HF (236). Currently, there is no reliable methods to diagnose non-adherence in patients with HF.

Aims: To determine the prevalence of non-adherence in patients with HF using tandem mass spectrometry. To evaluate the associations between non-adherence and clinical outcomes. To assess the cost-effectiveness of non-adherence testing using tandem mass spectrometry in routine care of patients with HF.

Design: Retrospective cohort study

Methods: The study population will be patients enrolled in the BIOSTAT-CHF who have stored urine samples available. BIOSTAT-CHF (A systems BIOlogy Study to TAilored Treatment in Chronic Heart Failure) is a large multi-centre prospective observational study involving 2516 patients in 11 European countries (237). The study aimed to characterise biological pathways related to response or no response to guideline recommended pharmacological therapy for CHF. The data on non-adherence will be correlated with existing demographic and outcome data from the BIOSTAT-CHF study. Cost effectiveness will be analysed using health-economic methods.

13.4 Conclusion

Frailty and malnutrition in patients with HF is complex and challenging to manage. Exercise therapy and nutritional supplementation might be potential treatment strategies. Complex interventions with input from a multi-disciplinary team and individualised therapies (combining exercise therapy, dietary advice, medication reviews and management of co-morbidities) might provide a more holistic approach to combat frailty and malnutrition. Further large-scale RCTs are needed to clarify the effectiveness of such interventions in patients with HF.

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