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An Examination of Heart Failure Rehospitalisation in a Western Metropolitan Melbourne Population

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Abstract

Heart failure is a complex clinical syndrome, associated with a significant burden of morbidity and mortality, including a high rate of rehospitalisation. Reducing the burden of rehospitalisation among patients with heart failure is a recognised priority for healthcare systems. However, in order to optimize outcomes, contemporary studies have emphasized the need for better understanding of the clinical heterogeneity of heart failure populations. Extending beyond the understanding of pathophysiological heterogeneity, the elucidation of sociodemographic factors may also reveal greater opportunities for targeted optimisation. Moreover, utilising new methods by which rehospitalisation is assessed may lead greater insights than would otherwise be captured by conventional means.

This project aims to expand the understanding of rehospitalisation burden in evolving heart failure populations. It evaluates the adverse impact of cultural and linguistic diversity on rehospitalisation outcomes in patients with heart failure. A discussion of important methodological concepts into researching culturally and linguistically diverse (CALD) patient groups is carried out. In doing so, a novel operational approach to defining CALD patients is presented.

This thesis also explores the measures of which rehospitalisation is evaluated in heart failure patients. It described the added value of analysing all recurrent hospital admissions (events), an approach which is very seldom performed in heart failure research. An assessment of several modelling techniques for evaluating rehospitalisation burden is performed, specifically in relation to heart failure type (i.e. heart failure with preserved vs reduced ejection fraction). In doing so, demonstrate the analysis of recurrent hospitalisations, compared to traditionally utilised first-event statistical approaches, may be a more informative and clinically relevant measure when evaluating the burden of heart failure rehospitalisation.

As the prevalence of heart failure is rising and patients are becoming more diverse and complex, there is an increasing need to better characterise and understand these evolving heart failure populations. Further elucidating the heterogeneity of heart failure populations will help guide improvements to existing management approaches, as well as the direct the development of new targeted approaches.

Declaration

This is to certify that:

(i) The thesis comprises only my original work towards the Master of Medicine, except where otherwise indicated and referenced,

(ii) Due acknowledgement has been made in the text to all other material used,

(iii) The thesis is less than 50 000 words in length, exclusive of tables, maps, bibliographies and appendices.

Dr Michael Seman

10th April 2020

Preface

This work is original, except where acknowledgements and references are made to previous work. This thesis contains data from clinical and administrative health datasets which is collected routinely by hospitals. Data analysis was performed with the aid of biostatistician Dr Koen Simons. Study concept, design, additional data collection and dataset management (including data cleansing, abstraction and linking), as well as writing and revision of the manuscript and the thesis were all performed in the vast majority by myself. Chapter 3 contains a significant amount of material from a published manuscript titled "*The impact of cultural and linguistic diversity on hospital readmission in patients hospitalized with acute heart failure*", which was published in the European Heart Journal - Quality of Care and Clinical Outcomes in April, 2020 (6,2:121-129). I was the first author of manuscript and contributed to greater than 90% of all aspects of study, including the manuscript writing. A copy of the manuscript can be found in the Appendix (appendix 7.1).

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Finally, I'd like to take this opportunity to express my gratitude to my partner Michelly for her amazing support and encouragement.

Manuscripts submitted during candidature

1. Seman M, Karanatsios B, Simons K, Falls R, Tan N, Wong C, et al. The impact of cultural and linguistic diversity on hospital readmission in patients hospitalized with acute heart failure. European heart journal Quality of care & clinical outcomes. 2020;6(2):121-9.

2. Mulligan A, Seman M, Abramowski R, Falls R, Scholes E, Vogrin S, et al. Cardio-geriatric model of care in acute heart failure: initial experience of a multidisciplinary approach in complex elderly patients. Internal medicine journal. 2020;50(4):488-92.

3. Biswas S, Seman M, Cox N, Neil C, Brennan A, Dinh D, et al. Impact of limited English proficiency on presentation and outcomes of patients undergoing primary percutaneous coronary intervention for ST-elevation myocardial infarction. Internal medicine journal. 2018;48(4):457-61.

4. Falls R, Seman M, Braat S, Sortino J, Allen JD, Neil CJ. Inorganic nitrate as a treatment for acute heart failure: a protocol for a single center, randomized, double-blind, placebo-controlled pilot and feasibility study. Journal of translational medicine. 2017;15(1):172.

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1. CSANZ Oral presentation for session *Heart Failure - It's not all about the drugs.* The impact of limited English proficiency on hospital readmission rate in culturally and linguistically diverse patients hospitalised with acute heart failure. 2017.

2. CSANZ Mini-Oral presentation. Comparison of Measures of Rehospitalisation Burden in Heart Failure with Reduced versus Preserved Ejection Fraction. 2018.

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List of tables and figures

List of Abbreviations

ACC	American College of Cardiology
ACE	Angiotensin Converting Enzyme
AED	Admitted Episodes Dataset
AHA	American Heart Association
ARB	Angiotensin II Receptor Blocker
ARNI	Angiotensin Receptor-Neprilysin Inhibitor
CALD	Culturally and Linguistically Diverse
CCMI	Charlson Comorbidity Index
CI	Confidence Interval
cMRI	Cardiac Magnetic Resonance Imaging
CSANZ	Cardiac Society of Australia and New Zealand
ED	Emergency Department
EDIS	Emergency Department Information System
EF	Ejection Fraction
EP	English Proficiency/Proficient
ERR	Event Rate Ratio
ESC	European Society of Cardiology
ESCHFA	European Society of Cardiology Heart Failure Association
HARP	Hospital Admission Risk Program
HF	Heart Failure
HFmrEF	Heart Failure with Mid-range Ejection Fraction
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
HR	Hazard Ratio
ICD	International Classification of Diseases
ICD-10-AM	International Classification of Diseases-10th Edition-Australian Modification
IHPA	Independent Hospital Pricing Authority
iPM	i.Patient Manager
LEP	Limited English Proficiency/Proficient
LOS	Length of Stay
LVAD	Left Ventricular Assist Device
LVEF	Left Ventricular Ejection Fraction
MRA	Mineralocorticoid Receptor Antagonists
NHFA	National Heart Foundation of Australia
OR	Odds Ratio
PACS	Picture Archiving and Communication System
PAS	Patient Administration System
SA1	Statistical Area Level 1
SD	Standard Deviation
SEIFA	Socio-Economic Indexes for Areas
TAVI	Transcatheter Aortic Valve Implantation

1. CHAPTER 1: Introduction

Heart failure (HF) has been singled out as a rising global epidemic and a major public health problem [1, 2]. At present, it is estimated 2% of the developed world's population live with chronic HF [3]. For such patients, the outlook is poor, with the major consequences of HF being disabling symptoms, repeat hospitalisation due to worsening of HF and premature death [4]. In the United States, HF is responsible for more than 1 million hospital admissions annually. And among developed countries it is the most common cause for hospitalisation in patients aged over 65 years [5, 6]. Despite contemporary pharmacological and device-based therapies improving patient symptoms and long-term survival, the problem of recurrent hospitalisation remains a prevailing issue for patients and healthcare systems [7].

The characteristics and heterogeneity of HF populations are evolving. Shifting demographics and epidemiological transitions are resulting in both an increasing number and a growing complexity of patients with HF [6]. In order to optimise patient outcomes, contemporary studies have emphasised the need for better characterisation and understanding of the heterogeneity of failure heart populations [8-11]. Extending beyond the understanding of pathophysiological heterogeneity, the elucidation of sociodemographic factors may also reveal greater opportunities for targeted optimisation. Moreover, utilising new methods by which patient outcomes are assessed may lead greater insights than would otherwise be captured by conventional means.

HF is a chronic disease, which can be complex for patients to self-manage. This complexity is only further complicated by poor health literacy, cultural idiosyncrasies and language barriers. Such challenges are commonly faced by marginalised ethnic and racial minority groups, also known as culturally and linguistically diverse (CALD) groups. Evidence demonstrates that CALD groups suffer from poorer health and utilise health services less compared to the general population [12-14]. Limited English proficiency (LEP), cultural differences, poorer health literacy, social isolation, financial constraints and discrimination are some of the barriers that impact on the health and well-being of CALD groups [12, 13, 15-20].

Australia is a culturally and linguistically diverse country. Over a quarter (26%) of Australia's 24 million population were born overseas, and of these first-generation Australians more than half (53%) speak a language other than English at home. The majority (82%) of the overseas-born population live in the capital cities, such as Melbourne, Sydney and Perth, where the proportion of overseas-born people

account for one third of these cities' population [21]. In Australia, CALD populations are at an increased risk of developing some chronic diseases [22] and have been shown to have increased barriers to accessing health care [16, 23-25]. Despite this, there are limited studies exploring health outcomes in CALD groups within Australia. In 2015 the Independent Hospital Pricing Authority (IHPA) published a costing study of CALD patients to inform a policy decision for whether an adjustment is warranted to the government healthcare pricing for CALD patients. The analysis indicated that at the national level the health costs incurred by CALD patients were not materially different from non-CALD patients, and if any disparity was present it can be accounted for by lack of interpreter services where required [26]. The authors noted that there were few Australian studies and data available, which impacted on the conclusions drawn in the report. In short, the Australian government is of the contention that despite CALD patients having barriers to healthcare their health outcomes, particularly healthcare utilisation, is comparable to the general (non-CALD) population and thus no additional healthcare funding or provision of resources (beyond interpreter services) are required.

As the prevalence of HF is rising within populations that are themselves becoming more diverse and complex, there is an increasing strain being placed on hospitals and wider healthcare systems. As such, there is a growing need to initially well characterise HF populations, as well as identify the any patient group health disparities that may be suffered amongst them. Only by first identifying and establishing evidence of disparities can the necessary steps be taken to address them.

This thesis presents a background and literature review to chronic HF, with particular focus on rehospitalisation outcomes. The first and principle study presented in this thesis evaluates the impact of cultural and linguistic diversity on HF rehospitalisation in a Western Melbourne population in Australia. And in doing so, discusses important methodological concepts and challenges in researching CALD populations, especially within the context of utilising administrative datasets.

The second study presented in this thesis examines the use of different methods to measure rehospitalisation in a HF population, presenting a novel recurrent event analysis approach. The study compares traditionally utilised first-event statistical approaches and an analysis of all recurrent events approach. To illustrate the different statistical methods to assess rehospitalisation burden, patients were evaluated according to HF type (i.e. heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF)), which is a very commonly investigated HF patient category. The inclusion of all recurrent hospitalisations (total events), beyond just the initial first-event (which is the most frequently utilised in HF research), allows for the capturing of a

representation of the true burden of disease – leading to the reveal of additional insights and greater demonstrative effect sizes between studied groups [27, 28].

This thesis focuses on rehospitalisation in vulnerable HF patients, who are increasing in number and complexity within the Australian population. Only by first identifying and further understanding the differences in these groups can the appropriate health resource provision and health policy initiated, along with research into effective strategies, to mitigate any disparities be identified. The research presented within this thesis hopes to inform future studies and health policy that examine rehospitalisation burden in HF populations, as well as health disparities of CALD groups in any disease context.

2. CHAPTER 2: Background and literature review

2.1. The definition of heart failure

Over the past twenty years the definition, classification and terminology of heart failure has evolved. This thesis primarily utilises the definitions and classification described in the National Heart Foundation of Australia (NHFA)/Cardiac Society of Australia and New Zealand (CSANZ) [29] and the European Society of Cardiology (ESC) guidelines [30, 31], and to a lesser extent by the by the American Heart Association (AHA)/American College of Cardiology (ACC) guidelines [32, 33]. Heart failure is defined as a complex clinical syndrome that results from any abnormality of cardiac structure or function that leads to failure of the heart to deliver oxygenated blood to the tissues at a rate commensurate with the metabolic requirements, or it does so only at the expense of elevated ventricular filling pressures [29-31, 33]. The inability of the heart to fulfil the demands of the tissues and/or elevated intracardiac pressures results in a multitude of clinical signs and symptoms. The cardinal symptoms of HF that patient's experience are breathlessness and fatigue [33].

2.1.1. Clinical symptoms of heart failure

The typical symptoms of HF, include breathlessness (or dyspnoea) on exertion, decreased exercise tolerance, orthopnoea, paroxysmal nocturnal dyspnoea, fatigue, ankle swelling, bendopnoea and as the syndrome progresses dyspnoea at rest [29, 31, 34]. Less typical symptoms, are nocturnal cough, wheezing, weight gain (>2kgs), feeling of being bloated, depression, palpitations and syncope [31]. If a patient has had HF for prolonged period they are described as having *chronic* HF [35, 36].

2.1.2. Clinical signs of heart failure

The signs of HF (and are also more specific for HF) include elevated jugular venous pressure, hepatojugular reflux, additional third heart sound and laterally displaced apex beat. Less typical (and less specific signs), include weight gain (>2kgs), peripheral oedema, lung crepitations, cardiac murmurs, tachycardia, irregular pulse, tachypnoea, ascites, hepatomegaly, pleural effusions (reduced basal breath sounds and dullness to percussion at the lung bases), narrow pulse pressure and cachexia and weight loss (in advanced HF). These signs of HF are also related to the underlying structural and functional cardiac abnormalities found in the patient [29, 31].

2.1.3. Cardiac structural and/or functional abnormalities in heart failure

The hallmark abnormality found in HF patients in left ventricular systolic dysfunction or diastolic dysfunction (or both). Any abnormalities of cardiac structures, including pericardium, myocardium, endocardium, great vessels or heart valves, as well as abnormalities of heart rhythm of the conduction system can result in or be contributory to the clinical syndrome of HF [33]. Such abnormalities can directly or indirectly result in impairment of left ventricular function or elevated intracardiac pressures (or both).

Cardiac function and structural abnormalities are most commonly assessed with echocardiography, however additional methods include cardiac catheterization, cardiac magnetic resonance, cardiac computed tomography, single-photon emission computed tomography, radionuclide cardiac imaging and bone scintigraphy [29, 37].

Left ventricular ejection fraction (LVEF) has historically been the most utilised measure of left ventricular systolic function. The ejection fraction (EF) is the percentage of blood volume that is ejected out of the ventricle per heartbeat. The EF can be calculated subtracting the end systolic volume from the end diastolic volume and dividing this by the end diastolic volume. The assessment of EF is subject to interobserver variability, as well as a degree of methodological imprecision and inaccuracies [38]. This is of particular importance as the LVEF is central to the categorisation of the HF types.

2.2. Heart failure terminology

2.2.1. Different heart failure types

The classification of HF types is based on the measurement of LVEF, the presence of structural heart disease, evidence of diastolic dysfunction with high ventricular filling pressures, and biomarkers (elevated natriuretic peptide levels) [31, 37]. The classification of HF type has evolved in recent years. And among the numerous guidelines which outline the classification of HF types, there are some subtle (yet important difference). This thesis adopts the HF type classification definitions and criteria outlined in the National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Guidelines for the Prevention, Detection, and Management of Heart Failure in Australia 2018 [29].

2.2.2. Heart failure with preserved ejection fraction (HFpEF)

The criteria for a diagnosis of HFpEF is the presence of symptoms of HF with or without accompanying signs of HF, AND a measured LVEF of greater than or equal to 50%, AND either objective evidence of either relevant structural heart disease (i.e. left ventricular hypertrophy or left atrial enlargement) or diastolic dysfunction without an alternative cause.

Diastolic dysfunction refers to the identification of high left sided intracardiac filling pressures. Evaluating for diastolic dysfunction is most commonly performed by echocardiography, principally via the measure of left atrial volume, mitral inflow velocity and mitral annual velocity. Additionally, invasive measures of intracardiac pressures either via measure of left ventricular (LV) end diastolic pressure or pulmonary capillary wedge pressure (which reflects left atrial pressure). Finally, the measuring natriuretic peptide levels with rule-in cut-offs values are also used [29].

2.2.3. Heart failure with reduced ejection fraction (HFrEF)

The criteria for a diagnosis of HFrEF is the presence of symptoms of HF with or without accompanying signs, AND a measured LVEF of less than 50%. In patients who have only a mildly reduced LVEF (41% to 49%), additional criteria is required; these are, signs of HF or objective evidence of left sided intracardiac filling pressures (as described in the HFpEF criteria above) [29]. In the ESC and AHA guidelines, the latter intermediate range (EF of 41 – 49%) is classified as a separate group [31, 33], where and the recently coined term of *heart failure with mid-range ejection fraction* (*or HFmrEF*) has been used.

2.2.4. Ejection fraction 40-50%

The main rationale of the 2016 ESC authors for separately identifying the proposed HFmrEF group, is so it can stimulate further research into what is a heterogenous group of patients [31]. The writing committee of the 2018 NHFA/CSANZ addressed in the guidelines why they had not also adopted a third intermediate group. The main reasons are that HFrEF and HFpEF have different clinical spectrums and postulated underlying pathophysiology, whereas in the proposed HFmrEF group no such clear clinical or pathological spectrum currently recognised. Additionally, the window of EF (41-49%), may be too narrow to confidentially assign patients to a separate HF group. Finally, at this stage it is unclear how the separate group can augment current clinical practice [29]. The NHFA/CSANZ guidelines appear to have a more pragmatic approach to the classification, where the emphasis is placed on clinical

management. The ESC guidelines, on the other hand convey great value on furthering the knowledge of this intermediate group.

Acute and chronic heart failure

- **Chronic heart failure** is an overarching term that refers to those patients with long-standing HF. Generally, patients with chronic HF have had a diagnosis of HF before (a minimum period of 3 months is arbitrarily ascribed) [29] and typically they have received some HF therapy.

- **Acute heart failure** refers to the manifestation of HF signs/symptoms that are gradually/rapidly worsening or of new-onset. It is a life-threatening condition that requires urgent treatment and typically leads to urgent hospitalisation [35, 36]. Acute HF can present in two forms; i) as the newly arisen or first occurrence of HF (de novo HF), and ii) as the acute decompensation of patients with pre-existing HF (or chronic HF) [39].

Chronic HF represents the state of disease long-term stability with possible gradual disease progressive. Conversely, acute HF represents the state of rapid deterioration and instability. Acute HF and chronic HF represent to different temporal states of a patient's HF clinical course and disease progression [39]. These two different states require very different approaches to management. One of the very principles of chronic HF management is for the prevention of episodes of acute HF or acute decompensation.

The use of 'heart failure' terms, especially the term *heart failure* itself, can be nuanced and their precise meaning by the user may only be evident in the context for which it is used. For example, in the acute hospital setting if one were to describe a patient as having "*presented via ambulance with heart failure"*, in this context the user essentially means '*acute heart failure'.* Additionally, often the term '*heart failure*' is used interchangeably for '*chronic heart failure',* particularly in reference to patients, however the user is indeed referring to '*chronic heart failure', e.g. "The use of ACE inhibitors in the management of heart failure".* However, more accurate language will be often be used when distinction of and specifying of sub-groups and temporal states are pivotal e.g. "*The inpatient initiation of sacubitril–valsartan in patients with HFrEF hospitalised with acute decompensated heart failure".* In this thesis, the use of the term '*heart failure*' (HF) may be used in place of '*chronic heart failure*', however not where clarity in the distinction of concepts and facts are essential.

2.3. Aetiology and pathophysiology

The aetiologies of HF vary considerably between high-income and developing countries. The most common causes of HF in developed countries are coronary artery disease and hypertension. Low-income regions on the other hand are have disproportionally affected by rheumatic heart disease and myocarditis. As a consequence, tailored approaches have been developed in patient management, public health strategies and policy for a given national context [6]. Concerning HF type, contemporary studies from developed nations have shown HFpEF and HFrEF to be equally represented in overall HF cases [40]. The aetiologies and pathophysiologies of HF according to HF type (HFrEF and HFpEF) are presented.

2.3.1. Heart failure with reduced ejection fraction

There are many aetiologies of HF (see Table 2.3), many of which a coincide with the risk factors for developing HF. When attributing a cause to HF, it is important to acknowledge that multiple causes frequently co-exist and interact in any given patient [2]. The aetiologies and pathophysiology of HFrEF is well characterised and better understood than in HFpEF. The vast majority of identifiable causes of HF (as outlined in Table 2.3), result in impaired LV systolic function and reduced EF, and hence are associated with the HFrEF group. Coronary artery disease for example are the most common causes of HFrEF (in developed countries) [38].

The cardinal abnormality in HFrEF is impairment of left ventricular systolic (or pump) function, resulting in reduced forward flow, impaired capacity to meet the end organ demands. This in turn results in a cascade of neurohumoral compensatory mechanisms aimed to improve blood volume to the heart. Activation of the renin-angiotensin system results in decreased salt and water excretion from the kidneys and peripheral vasoconstriction, leading to increase blood volume. The sympathetic nervous is activated, resulting in increased heart rate and peripheral vasoconstriction, as a means to maintain or increase cardiac output. These compensatory processes lead to only worsening of the mechanical environment of the heart. There is further left ventricular remodelling, progressive fluid accumulation (with symptoms and signs of congestion) [41, 42]. This pathophysiological cycle drives the progression of chronic HF, as well as an increasing susceptibility to episodes of rapid decompensation where patients present to hospital in an acute HF state.

2.3.2. Heart failure with preserved ejection fraction

Compared to HFrEF, the mechanisms and aetiologies that drive this are not well understood. It is widely accepted that HFpEF is a heterogenous complex clinical syndrome that encompass a number of pathophysiological processes across multiple organ systems. It is proposed that the presence of variety of clinical risk factors (e.g. advanced age, female sex) including cardio-metabolic diseases (e.g. diabetes, obesity, hypertension and chronic kidney disease) triggers and perpetuate a systemic proinflammatory state. This in turn, results in a cascade of systemic and microvascular inflammatory mediator release, leading to diminished nitric oxide levels, abnormalities in peripheral skeletal muscle oxygen delivery and metabolism, microvascular rarefaction, endothelial dysfunction, cardiomyocyte hypertrophy and stiffness, and myocardial interstitial fibrosis [43, 44]. Impairment of LV relaxation and diastolic function ensues, with or without left ventricular hypertrophy, and subsequent increased left sided intracardiac filling pressures. The increase of left atrial pressures, (which may only occur on exercise) leads to elevated pulmonary pressures and pulmonary congestion. This than results in the typical symptoms of breathlessness. In comparison to HFrEF, patients are less likely to have clinical manifestations of refractory fluid overload (e.g. ascites, anasarca, peripheral oedema), except when concomitant right ventricular dysfunction is present.

Whilst LV ejection fraction is preserved in patients with HFpEF (i.e. ≥50%), LV systolic function may indeed not be normal. Studies examining longitudinal systolic function, by measurement of strain (or deformation), have identified that LV global longitudinal strain is significantly altered in high proportion of patients with HFpEF [45, 46]. Additionally, it is shown to have a prognostic value in HFpEF patients, as it has been shown to be associated with worse long term mortality [47].

Left ventricular hypertrophy is commonly found in patients with HFpEF and can also be a marker of advanced hypertensive disease and/or that the hypertension is a prevailing factor in the patient's spectrum of HFpEF aetiologies. It is important to be aware that the left ventricular hypertrophy in patients with HFpEF can also be due to transthyretin amyloidosis. In a cohort of HFpEF patients with left ventricular hypertrophy, one study demonstrated wild-type transthyretin amyloidosis to account for 13% of cases. The authors suggested it is likely to be significantly underdiagnosed in HFpEF populations [48]. Such a diagnosis is particularly important to make due to the emergence of therapeutic options for transthyretin amyloidosis.

2.3.3. Ejection fraction 40-50%

In keeping with the principles conveyed in the NHFA/CSANZ 2018 guidelines [29] (discussed previously), this thesis does not look to make distinction of the intermediate range of HFrEF patients (EF 40-50%) and attempt to summarise the underlying aetiology and pathophysiology, which is separate from that of HFrEF and HFpEF.

It is important to appreciate, that the overarching aetiologies and pathophysiologies of both HFpEF and HFrEF, may best be conceptualised as two sides on the same spectrum; one which is highly complex and constitutes a multitude of interplaying factors. And the proposed intermediate *HFmrEF* group is very likely a representation of a mid-way segment of this spectrum.

Table 2.3 Causes of Heart Failure (adopted table from ESC 2016 and NHFA/CSANZ 2018 heart failure guidelines [29, 36])

Diseased Myocardium	
	Ischaemic: - coronary artery disease (infarction, ischaemia) - coronary artery dissection or embolism - secondary myocardial scar - microvascular disease - myocardial stunning/hibernation
	Inflammation: - infection (bacterial, viral e.g. HIV, protozoa, parasites e.g. Chagas disease) - immune (autoimmune and hypersensitivity myocarditis, hypereosinophilic syndromes, and connective tissue disease)
	Toxic damage: - alcohol, clozapine - cytotoxic drugs (e.g. anthracyclines) and immunomodulating drugs (e.g. cetuximab) - stimulant drugs (e.g. amphetamines, cocaine) - radiation - heavy metals (e.g. copper, iron, cobalt)
	Infiltration: - malignancy related (direct infiltration or metastasis) - amyloidosis - sarcoidosis - haemochromatosis or iron overload - glycogen and lysosomal storage diseases (e.g. Fabry disease)
	Metabolic derangements: - endocrinological (thyroid, growth hormone, cortisol, diabetes mellitus) - increased sympathetic drive (Takotsubo cardiomyopathy, phaeochromocytoma) - pregnancy and peripartum related - nutritional deficiencies (e.g., thiamine, selenium or iron) - malnutrition - obesity
	Genetic abnormalities: - dilated cardiomyopathy - hypertrophic cardiomyopathy - left ventricular noncompaction - arrhythmogenic right ventricular cardiomyopathy - muscular dystrophies
Abnormal Loading Conditions	
	Hypertension
	Valve and myocardium: - degenerative valve disease (e.g. aortic stenosis and mitral regurgitation) - rheumatic heart disease - congenital heart disease (e.g. ventricular septal defect)
	Pericardial pathology: - pericardial constriction or effusion
	High output states: - severe anaemia - sepsis - arteriovenous fistula - thyrotoxicosis
	Volume overload: - renal failure - iatrogenic fluid overload
Arrhythmias	
	Tachyarrhythmias: - atrial (e.g. atrial fibrillation) - ventricular arrhythmias
	Bradyarrhythmias: - sinus node dysfunction or conduction disorders

2.4. Management of chronic heart failure

The management of chronic HF involves evidence-based, multidisciplinary, patient-centred therapies, which aims to improve patient symptoms and quality of life, reduce mortality and prevent rehospitalisation. The management options for chronic HF differ according to HF type (HFpEF and HFrEF), where HFrEF has more proven therapeutic options then HFpEF. In this thesis the therapeutic options for HFrEF and HFpEF are discussed separately, however there is some overlap particularly in the nonpharmacological therapies.

Heart failure with reduced ejection fraction

The therapies of HFrEF can best be divided into three categories 1) pharmacological management, 2) non-pharmacological management, and 3) devices, surgery, and percutaneous procedures.

2.4.1. Pharmacological management

The inhibition of neurohumoral pathways such as the renin angiotensin aldosterone and sympathetic nervous systems forms the basis pharmacological therapies HFrEF. The cornerstone classes of pharmacological agents used are angiotensin converting enzyme (ACE) inhibitors, beta blockers and mineralocorticoid receptor antagonists (MRA). ACE inhibitors (e.g. perindopril and ramipril) and MRAs (e.g. spironolactone and eplerenone) modulate the renin angiotensin aldosterone system. Beta blockers (e.g. bisoprolol and carvedilol) exert their effect on sympathetic nervous. ACE inhibitors, MRAs, and beta blockers have strong evidence demonstrating a mortality benefit as well as a reduced risk for rehospitalisation in patients with HFrEF. An ACE inhibitor, beta blocker and MRA should be introduced as first line agents in all patients with HFrEF who have an EF of less than or equal to 40%, unless otherwise contra contraindicated or not tolerated. In patients with an ejection fraction between 40 – 50%, the benefit reaped from using ACE inhibitors, beta blockers and MRAs has shown not to be as strong compared to patients with an EF of less than or equal to 40%. However, commencement of these agents is still advised in this group albeit the recommendation is weaker. In patients who are unable to take an ACE inhibitor use of angiotensin II receptor blocker (ARB) (e.g. Candesartan) may be utilised, as the demonstrated benefits are similar.

Sacubitril/valsartan is a relatively new medication in a drug class called angiotensin receptor-neprilysin inhibitor (ARNI). Sacubitril (neprilysin inhibitor) inhibits the breakdown of vasodilatory natriuretic peptides leading to promotion of natriuresis (urinary sodium excretion), as well as effecting left ventricular remodelling. Valsartan is an ARB and acts to inhibit activation of the renin angiotensin aldosterone system. Studies have shown that in comparison to the ACE inhibition, sacubitril/valsartan reduces the rehospitalisation and mortality risk. Currently, the combination drug is recommended to be initiated following the maximisation of doses of first line agents and if the LVEF remains to be less than or equal to 40% (the existing ACE inhibitor (or ARB) must be ceased before commencement). Given it's demonstrated efficacy over an ACE inhibitor many believe sacubitril/valsartan to be a first line agent [(49)].

Ivabradine is a second line agent which acts to reduce the heart rate via the selective inhibition of the *funny Na channel* on pacemaker cells in the sino-atrial load. This drug has shown a mortality and rehospitalisation benefit in HFrEF patients (who were in sinus rhythm), however the mortality benefit was only demonstrated in patient who had a baseline heart rate of greater than or equal to 77. Its use is recommended in HFrEF patients with an EF of less than or equal to 35% and have a heart rate of greater than or equal to 70 and are who are on and ACE inhibitor and optimal tolerated dose of beta blocker.

For all HF drugs that have a proven benefit on rehospitalisation and mortality outcomes, it is important that there is gradual up titration of all agents to the maximally tolerated permitted dose used in the pivotal trial providing the evidence base – as it is likely there is a dose dependent benefit.

Loop diuretics (such as frusemide) are very frequently used for symptom management in patients with HFrEF to control fluid accumulation and reduce fluid congestion. Loop diuretics have not been rigorously studied in placebo control studies to explore an effect on rehospitalisation or mortality outcomes. However, they are greatly beneficial in the management of symptoms in HFrEF and are indispensable in the pharmacological armament for HF.

There are additional agents that may be of benefit when used in special populations, these include hydralazine, digoxin, nitrates and polyunsaturated fatty acids. The use of these agents is limited and specialised - and for the purposes of this thesis need no further elaboration on.

2.4.2. Non-pharmacological management

Evidence-based non-pharmacological strategies that have demonstrated to reduce hospitalisation and improve patient outcomes include 1) multidisciplinary HF management programs, 2) nurse led medication titration, 3) exercise training and 4) optimal multimorbidity management.

Multidisciplinary HF programs involve the integration of multidisciplinary workforce specialised in providing best care practices to HF patients. Teams comprise of a cardiologist or physician with an interest in HF, HF advanced practice nurses, pharmacists, community general practitioners, physiotherapist, occupational therapist, dietician, and psychologists, as well as palliative care physician, as required [29, 50-52]. The benefits seen in such a multidisciplinary approach is due to the bundled interventions that are implemented in a collaborative fashion. These programs typically focus on high-risk patients, especially those who have been recently discharged from hospital. As part of the program patients and their carers receive education about self-management of HF. Patients may start to receive support from the program during an admission for HF, with further care continuing as an outpatient [51-56]. Where face-to-face support is not available for patients in an outpatient setting, nursing lead home visitation, telemonitoring and over the phone support systems are utilised [29, 57].

Nurse led medication titration clinics have shown to be effective in reducing HF rehospitalisation, improving survival and the time to optimal dose titration of HF medications [57-59]. Nurse led clinics require an advanced practice nurse with expert knowledge in HF. These nurses are supported by a cardiologist or specialist physician and often work closely with patients' general practitioners. Telemonitoring and systems for telephone support are also utilised [29, 57, 59].

Regular exercise training of up to moderate intensity is shown to improve quality of life, decrease hospitalisation and improve physical functioning in in patients with HF [29, 60-63]. Whilst continuous endurance training may be most effective overall, resistance training is also of benefit particularly for maintenance of muscle strength in those who are risk of frailty and cachexia (e.g. in the advanced stages of HF) [62, 63]. Exercise training may require an initial period of supervision and can be embedded in cardiac rehabilitation programmes [29].

The vast majority of patients with HF are over the age of 65 and have multiple comorbidities [3, 64, 65]. Further to this, the number of comorbidities and their complexities tend to increase with age [66]. These comorbidities may hasten the progression of HF, and if any become unstable in their own right, may precipitate an episode of acute decompensation of HF [29, 67-69]. Hence, the optimal management of

comorbidities is essential in patients with HF [29, 36, 69]. Common comorbidities encountered in HF and their management importance in the context of chronic HF are presented in Table 2.4.

Table 2.4. Comorbidity Management Considerations in Chronic Heart Failure *(adapted from Atherton et al, 2019)*[69]

Comorbidity	Management Considerations
Hypertension	▪ Avoid diltiazem, verapamil and moxonidine in patients with HFrEF. ▪ Optimal control of blood pressure is important in patients with HFpEF: an MRA with or without an ACE inhibitor or ARB are preferred.
Coronary artery disease	▪ Avoid diltiazem, verapamil, moxonidine in patients with HFrEF. ▪ Revascularisation may improve symptoms and health outcomes.
Atrial fibrillation	▪ Identify and treat reversible causes. ▪ Determine risk of stroke to guide need for anticoagulation. ▪ Beta blockers and digoxin are favoured for ventricular rate control. ▪ Amiodarone may facilitate attainment/maintenance of sinus rhythm. ▪ Consider catheter ablation for recurrent, symptomatic atrial fibrillation (particularly with newly diagnosed or worsening HFrEF).
Diabetes mellitus	▪ Aim for moderate glycaemic targets (HbA1c 7.1 to 8.0%). ▪ Metformin is usually first-line therapy. ▪ SGLT-2 inhibitors are recommended second-line therapy and are shown to improve outcomes in HFrEF patients. ▪ Avoid thiazolidinediones due to the risk of worsening heart failure.
Chronic kidney disease and hyperkalaemia	▪ Exclude reversible causes of worsening renal function (volume status, nephrotoxic drugs, renovascular disease, urinary outflow obstruction). ▪ Temporarily cease renin-angiotensin-aldosterone inhibitors if acute hyperkalaemia occurs (potassium >6 mmol/L). ▪ Consider dietary review and potassium binders for hyperkalaemia.
Obesity	▪ Consider weight loss strategies for severe obesity (BMI >35 kg/m^2).
COPD/asthma	▪ Beta blockers are safe in most patients with COPD. ▪ Asthma is a relative contraindication to beta blockers: favour cardioselective beta blockers. ▪ Inhaled antimuscarinic agents are preferred over beta-2 agonists. ▪ Minimise doses of oral corticosteroids (inhaled corticosteroids are preferred).
Sleep disordered breathing	▪ Consider positive pressure ventilation for symptom relief for patients with predominant obstructive sleep apnoea. ▪ Optimise HF management and avoid adaptive servoventilation due to increased mortality in patients with predominant central sleep apnoea.
Gout	▪ Consider colchicine, intra-articular steroids (unless anticoagulated) and brief oral corticosteroids for acute gout management. Then use allopurinol (or febuxostat if intolerant) coupled with dietary measures for gout prevention.
Arthritis	▪ Avoid NSAIDs (or use cautiously) if severely decreased LVEF or hyponatraemia. ▪ Use TNF inhibitors cautiously and only if HF symptoms are well controlled.
Depression	▪ Consider cognitive behaviour therapy, pharmacological therapy (SSRIs preferred) and exercise training.
Iron deficiency	▪ Monitor iron studies and full blood count in patients with persistent HFrEF and administering intravenous iron if iron deficient (iron deficiency = serum ferritin <100 mg/L or 100 to 300 mg/L with transferrin saturation <20%). ▪ Consider investigation for gastrointestinal pathology (especially if also anaemic).

Abbreviations: ACE = angiotension-converting enzyme; ARB = angiotensin receptor blocker;; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; Hb = haemoglobin; HF = heart failure; HFrEF = heart failure associated with a reduced left ventricular ejection fraction; HFpEF = heart failure associated with a preserved left ventricular ejection fraction; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; SGLT = sodium-glucose cotransporter; SSRIs = selective serotonin reuptake inhibitors; TNF = tumour necrosis factor.

2.4.3. Device therapies

Implantable cardiac resynchronization therapy has been shown to improve patients' symptoms, and reduce morbidity and mortality in appropriately selected patients [31]. Patient with a QRS duration ≥130 milliseconds on electrocardiography and a concomitant LVEF measured at ≤35%, despite being treated with optimal medical therapy should be considered for cardiac resynchronization therapy. Patients implanted with cardiac resynchronization therapy are often also implanted with an implantable cardioverter defibrillator. An implantable cardioverter defibrillator is recommended for secondary prevention (i.e. in patients who have recovered from documented ventricular arrhythmias or sudden cardiac death) to reduce the risk of sudden death in those patients who have a life expectancy of greater than 1 year and have a good function status. An implantable cardioverter defibrillator is recommended for primary prevention in patients with an LVEF of ≤35% despite a period of at least 3 months of being on optimal HF therapy [31].

2.4.4. Surgical and transcatheter options

Depending on the causative or contributory aetiology present patients may benefit for surgical or percutaneous interventions. For patients with significant coronary artery disease, surgical revascularisation with coronary artery bypass grafting or percutaneous intervention (i.e. stenting of coronary arteries provide has demonstrated significant improvements in morbidity and a trend towards improved survival [70-73]. The decision of surgical vs percutaneous revascularisation is dependent on the extent of disease (i.e. number of vessels involved), whether the patient has diabetes, and whether the anatomy favours one approach over the other. Typically, patients who have multivessel coronary artery disease, who are also diabetics and do not have a prohibitively high risk for surgery, would be gain most benefit from surgical revascularisation rather than percutanous [29, 31, 73, 74].

In symptomatic patients with severe valvular disease that, in particular aortic valve disease (aortic stenosis and/or regurgitation) and mitral valve disease (mitral stenosis and/or regurgitation), surgical valve replacement or repair is often indicated [29, 31, 75]. In patients who are too high risk for surgery, transcatheter options may be available, such as transcatheter aortic valve implantation (TAVI) for severe aortic stenosis and mitral-clip for severe mitral regurgitation [76-80]. Transcatheter options for valvular heart disease is an evolving area where indications for interventions are expanding.

HF secondary to congenital heart defects may also be amenable to corrective surgical or transcatheter intervention [81-83]. For example, atrial septal defects and ventricular septal defects can be closed surgically with a bioprosthetic patch or via a transcatheter umbrella closure device [84-86]. The particular approach is highly dependent on whether the anatomy favours one approach over another [87].

2.4.5. Heart transplantation and mechanically assisted circulatory support

Heart transplantation is considered to be appropriate treatment option in select patients with end-stage HF and where all other therapeutic options have been exhausted. Heart transplantation considerably increases patient's long-term survival and quality of life compared to conventional treatment. Mechanical circulatory support, such as Left Ventricular Assist Device (LVAD), may be considered in patients with refractory end-stage HF and despite optimal medical therapy have persistent symptoms. An LVAD may be used to reduce the risk of HF rehospitalisation and sudden death in such patients. LVADs are frequently used as a bridge to heart transplantation or a bridge to HF transplant consideration. The use of heart transplantation and LVADs in the treatment of end-stage HF is a highly specialised, which is conducted by only five hospitals in Australia [88]. Further details relating to the indications and management practices of heart transplantation and LVADs are not presented in this thesis as it is beyond the scope.

2.4.6. Palliation and end of life care

Palliative care has been shown to help alleviate the symptoms associated with end-stage HF and improve overall patient and family member satisfaction with the care they receive [89]. Early introduction of palliative care should be considered in all patients with end stage HF. However, it can be difficult determining whether patients are in the end stage of disease. In these patients, it is imperative to ensure that all reversible causes of HF have been excluded, best medical therapy has been optimised and any alternative treatment options (e.g. transplantation) have been explored. Advance care planning may be part of the palliative care process or may be introduced prior to the introduction of palliative care. Advance care planning has been shown to improve quality of life and patient satisfaction in end of life care [90]. The emphasis of palliative care lies in the addressing of supportive needs and symptom management of the patient. Effective communication between the patient, family members and health professionals is essential to ensure all involved share a common understanding of the goals of treatment. Palliative care is typically approached in multidisciplinary fashion, involving Cardiologists, HF nurses, palliative care physicians and palliative care nurses, as well as general practioners [91]. Despite a body of evidence to show the benefits of palliative care in HF

patients, it is often underutilized and is not incorporated into standard practices of HF management [89].

2.4.7. Therapies for heart failure with preserved ejection fraction

Unlike HFrEF, there are limited evidence based therapeutic options available for HFpEF. Current guidelines, recommend the use of loop diuretics to manage symptoms of congestion. There should be the identification and active management of comorbidities such as hypertension, chronic obstructive airways disease, diabetes and atrial fibrillation [29, 31]. Regular exercise has shown to improve patient symptoms, however not to the extent as is seen in HFrEF [60]. The only pharmacological agent to have shown some benefit in patients is spironolactone. Spironolactone was associated with reduced rate of HF rehospitalisation, additionally there was a trend for improved mortality, however this was not statistically significant [92].

2.5. Epidemiology of heart failure

2.5.1. The global burden of heart failure

Worldwide HF is an increasingly growing major public health problem and is estimated to affect 2% of the developed world's population [3]. Whilst HF affects individuals of any age, it is significantly over-represented in elderly patients. The estimated prevalence of HF in 40-year-old individuals is 1%, compared to 10% in individuals aged 75 years and greater. In the United States (US), HF is the leading reason for hospital admission among patients over 65 years of age, and in total is responsible for over 1 million hospital admissions annually [93]. Patients hospitalised with acute HF have an overall 4% in-hospital mortality [94]. Despite steady improvements in survival trends in many parts of the world [95] [4, 96, 97], the overall prognosis for patients with chronic HF remains poor, with 5-year mortality rates still up to 50% in most age-groups [98, 99]. And premature life years lost are comparable, if not greater (in both sexes), than the most common forms of cancer [100].

2.5.2. Global incidence and prevalence

The prevalence of HF is estimated to be 38 million individuals globally. In recent decades the prevalence of HF has been increasing and has been described as a rising epidemic [6]. The increasing

prevalence is reflective of improved survival in acute cardiac illnesses and in heart failure patients themselves, coupled with the increasing incidence in an aging population. As the risk of HF increases with age, an overall longer life expectancy in the population results in an increasing incidence and prevalence of HF in an aging population. In addition, there is an increasing incidence associated with improved survival in patients with ischaemic heart disease. Improved survival in HF patients has also contributed increasing prevalence. The increasing number and availability of treatment options with mortality benefits (e.g. drugs and cardiac device therapies) has been the primary reason of improvement in survival trends [101].

Estimates on the world wide incidence and temporal trends of HF are considered to be lacking and unreliable [102]. Epidemiological estimates are derived from literature and data from primarily high-income and developed nations. In these countries the incidence of HF has demonstrates trends to stabilisation (and possible reduction). It is postulated that the main reasons for this trend are improvements to cardiovascular disease primary and secondary prevention, along with improved treatments for ischaemic heart disease [6]. Overall, the global incidence of HF is estimated to be up to 10 per 1000 person years [103]. For both men and women, the lifetime risk of developing HF is estimated to be 20% between the ages of 40 and 80 years [6, 104].

Contemporary studies have shown HFpEF and HFrEF to be equally represented in overall HF cases [40]. However, HFpEF is more prevalent in the elderly and in patients with multiple co-morbidities. Thus, as the population of HF patients are becoming older the proportion of HFpEF may be expected to increase [38].

2.5.3. Mortality

Long-term survival of HF patients has been shown to be comparable to some cancers such as colon cancer, and less than the survival rate of breast cancer [105]. After initial diagnosis of HF, the estimated survival is 72-75% at 1 year and 35-52% at 5 years [99, 101, 105, 106]. In-hospital mortality rate associated with a HF admission is 4-7% [107] [108, 109]. Following an admission for acute HF, estimated mortality rates at 30 days are 10% [106]. Survival rates are increasing however. Within the last thirty years survival rates of HF patients have increased by at least 1 year [107]. This trend reflects the increasing availability of improved pharmacological and device therapies for HFrEF, and not HFpEF. There are no available therapies for HFpEF that are associated with improved survival [44].

Among patients with HFpEF and HFrEF, mortality rates vary in the literature. Whilst some studies observed similar mortality rates among HF types [110, 111], others have shown a lower risk of death in HFpEF patients [29, 112, 113]. A 2012, meta-analysis showed a 3-year adjusted mortality rate of 32% for HFrEF and 25% in HFpEF patients [113]. Regardless, absolute mortality is still high in HFpEF; wherein no therapies are currently available that confer a reduction in mortality.

2.5.4. Hospitalisation in heart failure

Chronic HF is hallmarked by intermittent episodes of acute decompensation requiring treatment intensification and often hospitalisation [2]. Each acute admission for HF is associated with further deterioration of cardiac function and quality of life; thus, contributing to the progressive chronic decline seen in HF (see figure 1.5) [114].

In economically developed countries, HF (as a primary diagnosis) accounts for 1 - 4% of all hospital admissions diagnosis [4, 115]. It is the most common cause for hospital admission in patients aged over 65 years, which is then followed by pneumonia, cardiovascular disease and cancer [5, 6]. This estimate is likely to be a significant under-representation of the true burden, as HF may be recorded as a secondary diagnosis [4]. In recent decades, the rate of HF hospitalizations has steadily increased, especially in aging populations [5]. In the US, is responsible for over 1 million hospital admissions annually [93], and the number of admissions that included HF as a cause had tripled from 1979 to 2004 [5, 6].

Following discharge of an index admission due to HF, overall readmission rate at 30 days is between 17% and 27% [116-119]. Risk for readmission continue to increase in the long term, with overall (or all-cause) readmission rates estimated to be 44% at 6-months [120, 121] and up to 62% at 1 year [122]. Of these readmissions, approximately 30 to 50% are HF related and the remaining are due to non-HF causes [67, 116, 118, 122-124], which includes other cardiovascular causes (e.g. acute coronary syndrome).

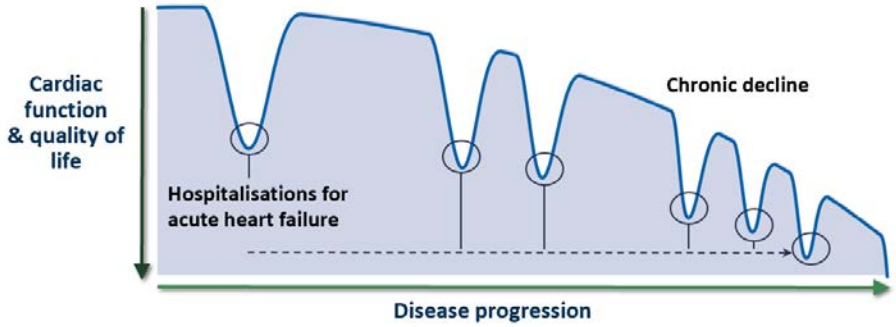

Figure 1.5. Chronic heart failure hallmarked by intermittent acute heart failure hospitalisation. Each acute event contributes to the chronic decline of heart failure. Following each admission for acute heart failure, there is short-term recovery, however with further deterioration of both cardiac function and quality of life. (*Adapted from Gheorghiade et al, 2005*) [114].

2.6. Risk factors for rehospitalisation in heart failure

A considerable number of studies have identified a wide variety of risk factors associated with rehospitalisation in HF. Many of the risk factors for rehospitalisation in HF are also predictors for developing HF, some of which are mechanistically the primary cause (e.g. alcohol consumption). The risk factors for rehospitalisation may be broadly grouped into either clinical or sociodemographic factors.

2.6.1. Sociodemographic

Increasing age is associated with an increase in HF rehospitalisation in both the short and long term. Annual readmission rates rapidly increase in beyond 60 years of age [125]. For patients aged 65 to 79 years there is more than a 3-fold increase in all-cause 30-day readmission rates, and for patients aged ≥ 80 years, there is a 4-fold increase [126] [68]. This increased risk is maintained when adjusting for known confounders. The influence of gender on rehospitalisation outcomes in HF has varied in the literature. Where HF subgroups (HFpEF & HFrEF) is not specified, an increase risk has been reported for both male [121, 127-129] and female gender [125, 130-132], and some studies have shown no significant difference [68] in rehospitalisation between genders [133] [68, 134, 135].

Numerous studies have demonstrated lower socioeconomic status portends to increase rehospitalisation in HF patients [127] [116, 117, 119, 136-139]. Single marital status (or lives alone), compared to married or de-facto has been reported as a predictor for rehospitalisation [140-142]. Sociodemographic

factors that are associated with increased mortality, but not increased rehospitalisation include level of health literacy and presence of social supports [117]. Patient race and/or ethnicity has repeatedly been shown to be associated with increased risk of rehospitalisation in HF patients [119, 121, 125, 132, 143, 144]. The evidence surrounding this is expanded upon in the section on cultural and linguistic diversity.

2.6.2. Clinical comorbidities

A large proportion of patients with HF have multiple co-morbidities, both cardiac and non-cardiac [68, 117, 119, 144, 145]. The number and complexity of these comorbidities mount with increasing age. The clinical comorbidities that have been identified as predictors for rehospitalisation in HF patients include chronic kidney disease [121, 144, 146], chronic lung disease [146], sleep apnoea [147], hypertension [142, 146], atrial fibrillation [129, 148], coronary artery disease or ischaemic heart disease [144], diabetes [144, 146] and malignancy [142, 146]. Many of these comorbidities associated with increased rehospitalisation are also predictors for developing HF, and are also directly implicated in the aetiology of HF (e.g. hypertension and ischaemic heart disease). Cognitive impairment and psychiatric diseases such as depression and anxiety have also been identified as risk factors for rehospitalisation in HF patients [149, 150]. Furthermore, it has been shown that an increasing number of comorbidities is independently associated with readmission risk [142, 146, 151].

Following a discharge from an index hospital admission for HF patients who have had a prior history of HF (i.e. not the de-novo presentation) have an elevated risk of earlier rehospitalisation [127, 128, 130]. In addition, patients who have had a recent admission (less than 6 months prior), for HF or any cause, are also at increased risk of rehospitalisation following discharge [68, 152, 153].

2.6.3. Heart failure in Australia

Estimates of the prevalence of HF in the Australia population were evaluated in a 2016 systematic review by Sahle and colleagues, who collated all available epidemiological data on population level HF studies [65]. The review concluded that the estimated prevalence of HF in Australia is between 1.0–2.0 %. This is in keeping with the prevalence seen in other developed nations [64, 154]. The incidence of HF in Australia is estimated to be 30 000 new diagnoses per year [155]. Those in Australia who are disproportionately affected by HF include, Indigenous rather than non-Indigenous Australians, in individuals from rural and remote regions rather than from capital city or metropolitan areas, and in those with socioeconomic disadvantage [65, 156]. There was evidence to suggest that HF is more prevalent in women than in men [65]. Similarly, to other high-income nations [64, 154], HF is more

prevalent amongst the elderly in Australia. With patients aged 65 years or over representing two thirds of those affected by HF [156].

The most common aetiology of HF (specifically HFrEF) in Australia is ischaemic heart disease, which is usually accompanied by a history of myocardial infarction. Other aetiologies include hypertension, valvular heart disease, idiopathic cardiomyopathy and alcohol related [156, 157]. The risk factors for developing HF in Australia are comparable to the established known risk factors in other developed countries (e.g. chronic kidney disease, diabetes, smoking, dyslipidaemia, smoking and alcohol), with the exception of rurality and being an indigenous Australian (discussed above) [157]. There is no evidence to suggest an increased burden of HF in ethnic or racial minority groups (CALD groups), which is seen in the US [6].

HF rehospitalisation and mortality rates in Australia are similar to that seen in other developed countries [155]. The all-cause mortality at 30 days and 365 days following first admission for HF is 8% and 25%, respectively. In Australia, hospitalisations due to HF is estimated to cost more than one billion dollars each year [155]. In 2014–15, there were 55,511 hospitalisations for HF (as the primary diagnosis), equating to 196 hospitalisations per 100,000 people (the Australian rate) [156]. High rates of rehospitalisation have been reported with 30-day and 365-day all-cause readmission rates of approximately 20% and 56%, respectively [155]. Data from Western Australia, demonstrate the trends of overall burden of HF hospitalization are increasing, particularly due to non-ischaemic causes [97] (where the evidence for effective therapies is especially limited) [31].

2.7. Measuring rehospitalisation in heart failure

Recurrent hospitalisation (or admission) in patients with HF poses a great burden on healthcare systems. The evaluation of rehospitalisation/readmission is widely utilised by clinical trials and in epidemiological studies to investigate, compare and monitor outcomes in patients with HF. However, multiple challenges are presented when embarking upon research that evaluates rehospitalisation. One of the most critical first steps is to secure a research definition for rehospitalisation. Once a definition is established, it can be difficult to decide upon the appropriate method or methods to measure rehospitalisation, for any given research question.

Despite extensive literature describing HF rehospitalisation, there is lack of clarity in the presuppositions and language used concerning rehospitalisation/readmission. This thesis section discusses the background and literature, concerning the definitions and measurement methods used

in the study of rehospitalisation in HF populations. In addition, a foreword is presented of important terminology and concepts when discussing rehospitalisation in a research context.

2.7.1. Definitions

The Oxford English Dictionary defines *definition* as a precise statement or explanation of the essential nature of a thing, or what a word means [158]. A conceptual (or constitutive) definition, pertains to the ideas, principles or essential general meaning of a construct or concept [159]. It is the definition which is representative the common or every-day meaning of a word or thing. In research, an operational definition ascribes meaning to a concept by specifying operations that must be performed in order to measure the concept as an observable variable. In doing so, operational definitions act to help bridge the gap between the theoretical and the observable [159]. Within the research space, the delineation between a conceptual and operational definition for key study variables are not always made clear, and as a result can be the source of confusion and inconsistent findings.

2.7.2. Defining rehospitalisation/readmission

Rehospitalisation as a broad concept can be defined as a hospital admission (or hospitalisation) that takes place following the discharge from an index or reference admission. However, the boarders of this conceptual definition are hazy. To some, rehospitalisation may only refer to hospital admissions that are of an emergent non-elective nature. Whilst others may consider non-emergent or elective/planned admissions to be inclusive of this definition. Additionally, the duration of hospitalisation, or what constitutes as *hospitalisation* is also unclear, and as a result raises many questions. For instance, is there a minimum amount of time required before an admission is considered admission? For instance, can an admission be 5 minutes in duration? Furthermore, when and where does an admission to begin and end? For example, in patients admitted from the emergency department, is time spent in the emergency department considered to be inclusive of the period of hospitalisation. Conversely, if a patient has been transferred to sub-acute care for rehabilitation, following an episode of acute HF, does the period in sub-acute care count to a single readmission episode? Likewise, if a patient's care (acute management +/- sub-acute care/rehabilitation) was transferred between two or more health care facilities, how this/these episode/episodes of hospitalisation are regarded across different health facilities may not be clear. The transitions of care may be regarded collectively as a part of a single episode of hospitalisation, or each period of care in each health care facility may be considered separately.

Whilst the everyday conceptual understanding of rehospitalisation may be subject to variation and blurred boarders, it is critical that definitions of rehospitalisation within research methodologies are comprehensive and clear. Despite the increasing incorporation of rehospitalisation as in study outcomes, it is frequently poorly, if at all, defined in research publications [160-163]. In addition, where definitions are provided, there is wide variation and inconsistencies among studies [160, 163-166].

In a health services research study, Chambers and Clarke operationally defines readmission *as 'the next subsequent admission of a patient as an immediate (that is, emergency or unplanned) admission… within a defined interval of a previous (index) discharge taking place within a defined reference period'* [160, 167]. This overarching definition of rehospitalisations is not specific to any disease/diagnosis or group of diseases/conditions, and hence represents rehospitalisation due to any cause i.e. all cause rehospitalisation.

2.7.3. Definition of heart failure rehospitalisation

The 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials define HF hospitalisation as '*the patient is admitted to the hospital with a primary diagnosis of HF where the length of stay is at least 24 h (or extends over a calendar date if the hospital admission and discharge times are unavailable), where the patient exhibits new or worsening symptoms of HF on presentation, has objective evidence of new or worsening HF, and receives initiation or intensification of treatment specifically for heart failure'*[168]. In a consensus document published by the European Society of Cardiology Heart Failure Association (ESCHFA), the authors defines HF hospitalisation as an '*admission into hospital requiring at least an overnight stay caused by substantive worsening of heart failure symptoms and/or signs requiring the augmentation of oral medications or new administration of intravenous heart failure therapy, including inotropes, diuretics, or vasodilators*' [169]. In this same document, the authors make note of the standardised definition put forward by the writing committee of the ACC/AHA Cardiovascular Endpoint Events report, and expressed that some experts raised concern that this too restrictive and may result in low sensitivity to detect HF events, leading to lower event rates and potentially loss of safety signals [169]. Both the aforementioned definition of HF rehospitalisation act as a both conceptual and operational definition within a clinical trial research framework. This is because what is required operationally are the features outlined in the definition to be directly observed or demonstrated at the patient level.

Research involving the utilisation administrative health care data to identify a HF hospitalisation (as well as other disease specific events), requires a specific operational definition that substitutes

diagnostic codes for the collective patient level features outlined in the ACC/AHA and ESCHFA definitions, which are clinical trial focussed. The most commonly used diagnostic coding is the World Health Organisation International Classification of Disease (ICD) [170]. Using ICD coding in administrative databases has been shown to be a validated method to identify HF and other clinical conditions [170-174]. The vast majority of validation studies, which involved comparing ICD coding to medical record review, show positive predictive values of >95% [172]. Examples of codes from ICD 10th edition Australian Modified (ICD-10-AM) which are used to operationally identify a HF admission include I50.0 (*Congestive heart failure*), I50.1 (*Left ventricular failure*) and I50.9 (*Heart failure, unspecified*) [175] (see Table 2.7). A multitude of HF studies have used ICD codes to identify episodes of HF hospitalisation [96, 155, 176-181]. In a systematic review of HF identification using administrative data, the authors reported a wide variation of algorithms (i.e. operational steps) to identify a HF admission amongst studies [172]. The kinds of variation to algorithmic approaches that were discussed in this review included; the predefined duration of in-hospital stay to indicate a hospitalisation, the inclusion of emergency department data and duration, the adjudicated HF diagnostic codes used, and the inclusion of hospitalisations where HF was a secondary diagnosis and not primary. Currently, there is no consensus on the operational definition/algorithm (including selection of range of ICD-10 diagnostic codes) to identify HF hospitalisation in administrative datasets.

Table 2.7. Commonly used ICD-10 codes used in operational definitions for heart failure hospitalisation hospitalisation (*adapted from Saczynski et al, 2012)* [172].

CODE	DESCRIPTION
I11.0	HYPERTENSIVE HEART DISEASE WITH HEART FAILURE
I13.0	HYPERTENSIVE HEART AND CHRONIC KIDNEY DISEASE WITH HEART FAILURE AND CHRONIC KIDNEY DISEASE STAGE I – STAGE IV OR
I13.2	HYPERTENSIVE HEART AND CHRONIC KIDNEY DISEASE WITH HEART FAILURE AND CHRONIC KIDNEY DISEASE STAGE V OR END STAGE RENAL
I25.5	ISCHEMIC CARDIOMYOPATHY
I42.0	DILATED CARDIOMYOPATHY
I42.5	OTHER RESTRICTIVE CARDIOMYOPATHY
I42.6	ALCOHOLIC CARDIOMYOPATHY
I42.7	CARDIOMYOPATH DUE TO DRUGS AND EXTERNAL CAUSES
I42.8	OTHER CARDIOMYOPATHIES
I42.9	CARDIOMYOPATHY, UNSPECIFIED
I43	CARDIOMYOPATH IN DISEASES CLASSIFIED ELSEWHERE
I43.0	CARDIOMYOPATHY IN INFECTIOUS AND PARASITIC DISEASES CLASSIFIED
I43.1	CARDIOMYOPATHY IN METABOLIC DISEASES
I43.2	CARDIOMYOPATHY IN NUTRITIONAL DISEASES
I43.8	CARDIOMYOPATHY IN OTHER DISEASES CLASSIFIED ELSEWHERE
I50	HEART FAILURE
I50.0	CONGESTIVE HEART FAILURE
I50.1	LEFT VENTRICULAR FAILURE
I50.9	HEART FAILURE UNSPECIFIED

2.7.4. Methods of measuring rehospitalisation

HF is a chronic condition that is hallmarked by repeated episodes of acute decompensation requiring hospitalisation. The repeated hospital admissions place a heavy toll on patients, families and health care systems – and accordingly is known as the *burden of rehospitalisation*. Rehospitalisation is a frequently utilised to assess outcomes in clinical trials and epidemiological studies, as well as for appraisal of performance in hospitals. There a numerous statistical method in assessing rehospitalisation, however the most frequently utilised involve the first-event approach. A systemic review that assessed statistical models for identifying risk of rehospitalisation after index admission for HF identified logistic regression followed by the Cox-proportional hazards model to be the most frequently utilised among studies. Logistic regression and Cox-proportional hazards models are both of methods that adopt an analysis of first-events only. Such approaches ignore all data of readmissions (events) subsequent to the first readmission. Hence, a first-event approach may not best represent the true burden of rehospitalisation for individuals or for healthcare systems, as it is not measuring the multiple, or recurrent readmissions, subsequent to the first readmission, which patients commonly experience during the course of their illness. In addition, repeated hospitalisation in patients with HF has been is an indicator of disease worsening [68, 121, 128]. In view of this, there has been increasing interest in adopting an analysis of recurrent events approach, whereby all rehospitalisation events experienced by the patient, over an observed time frame, are included in the method [182]. Statistical approaches with recurrent event endpoints are usually more complex however. Within clinical and epidemiological research, there are limited studies that have utilised these methods, in addition there is less industry and academic regulatory experience [183]. Statistical methods which have been utilised for assessing recurrent rehospitalisation include Poisson Regression, Negative Binomial, Andersen–Gill and Wei-Lin-Weissfeld models [27]. The Poisson Regression and Negative Binomial models and considered to be the simplest models to use for analysis of recurrent events[184]. These models, use the total number of events over a fixed period of time, and do not factor in individual difference in duration between repeated events [185]. Where factoring in differences in time between repeat events may be required (particularly where time-varying covariates or time-varying effects are considered to be substantial) the Andersen–Gill or the Wei-Lin-Weissfeld models can be utilised [185]. However, it remains unclear whether techniques accounting for time between repeat readmissions yield additional value, at the cost of greater complexity, when compared to the simpler Poisson and Negative Binomial models. Indeed, within the literate the use of these statistical techniques varies across studies, and there is no consensus on the preferred approach in any given context.

2.7.5. Recurrent event analysis in heart failure studies

There are a number of HF studies that have used incorporated analysis of all observed recurrent events in their statistical methodology [28, 186-194]. A study assessing the use of Ivabradine in patients with HFrEF, demonstrated a substantial reduction in the likelihood of recurrent hospitalizations in patients treated with Ivabradine on top of guideline-based therapy [188]. Randomized trials of cardiac resynchronization therapy have reported a reduction in recurrent rehospitalisation in patients with HFrEF [190, 195]. The Valsartan Heart Failure Trial (Val-HeFT) showed Valsartan compared to placebo resulted in significant reductions in HF rehospitalisation, where most benefit was demonstrated in recurrent hospitalizations [192]. Similarly, Enalapril, compared to placebo, was shown to reduce the proportion of patients who had multiple readmissions [191]. To highlight the value of evaluating recurrent events, there are studies that have compared first-event and recurrent event statistical approaches by performing post-hoc analyses of data from landmark clinical trials in HF (which originally did not have recurrent event endpoints). A post hoc-analysis of the EMPHASIS-HF study showed that Eplerenone markedly reduced the risk of recurrent HF hospitalizations to a greater extent than what was captured by only studying the time to first rehospitalisation only [186]. Likewise, a post-hoc analysis from the CHARM-Preserved trial, showed Candesartan reduced the rate of HF readmissions, and the reduction in rehospitalisation was seen to a greater extent in the analysis of all recurrent admissions than from the analysing only the first readmission [28]. The analysis of total recurrent events has also been increasingly utilised in epidemiological studies investigating risk factors for patient outcomes, including HF rehospitalisation and cardiovascular events [102, 123, 196, 197] [66, 198]. Ip and colleagues showed the for individuals with diabetes and who smoke, the overall attributable cardiovascular risk for these risk factors is estimated to be substantially higher when modelled with recurrent events compared to a first-event method only [66]. Due to the frequency of recurrent rehospitalisation, the possibility of multiplicative and additive effects associated with risks or treatments/interventions can be better detected with recurrent event analysis [199]. The inclusion of recurrent event analysis in clinical and epidemiological trials in HF is increasingly being advocated [28, 186, 188, 200].

2.8. Cultural and linguistic diversity

2.8.1. Definitions and concepts

In recent decades, accelerating global migration and urbanisation have given rise to rapid cultural and linguistic diversification of populations worldwide [201]. The term 'culturally and linguistically diverse' (CALD) is a broad descriptor for individuals and communities, who possess ethnic/racial, cultural, religious and/or language characteristics that are different to those of the majority, in a given national context [202]. In Australia, 26% of the population were born overseas - and of those born in Australia, 53% speak a language other than English at home [21]. In Australia¸ the US, Canada and the United Kingdom (UK) studies demonstrate that CALD groups suffer poorer health status compared to the general population [12-14, 203].

2.8.2. Defining CALD for research and data collection

Studying the health impact of cultural and linguistic diversity has the inherent challenge of no universally accepted definition for CALD. As a construct, CALD is complex and abstract, characterised by the multiple dimensions of culture, ethnicity, religion and language. Hence, the translation of the concept of CALD to its operationalisation in research and policy has varied. Traditionally, studies have addressed the concepts of 'ethnicity' (or 'race') and 'language discordance' as methodologically separate entities. Data collected on place of birth or self-identified racial/ethnic group has been used to categorise ethnicity/race [204].

In Australia, a commonly used definition for CALD amongst government bodies for the purposes for data collection is "*if two of the following criteria are met i) The individual or at least one parents is born overseas ii) The individual speaks a language other than English at home, iii) The individual has a culturally and linguistically diverse background"* [205, 206]. In this definition, "*born overseas*" may be considered too inclusive, as individuals or individuals born with parents born in and English-speaking predominant country such as New Zealand or England would satisfy this definition as being CALD. In addition, it is unclear what constitutes a "*culturally and linguistically diverse background"* in point 3. A report published by the Australian Institute of Health and Welfare examined measures of cultural and linguistic diversity within the aged care sector [206]. This report highlighted there was no standardised operational definition for CALD and that numerous Australian databases were inconsistently defining CALD and capturing measures of CALD. The authors recommended a minimum

of the following datapoints to be collected to identify CALD groups - *'Country of birth' and 'Main language spoken at home', augmented with 'Interpreter required', 'Preferred sex of interpreter' and 'Preferred language', where the main language is other than English.* In addition, *'Proficiency in spoken English' and 'Year of arrival'* (to Australia), as well as *linked measures associated with spirituality*, were also recommended data points for supplemental inclusion. The report did not explicitly put forward a standardised data definition for CALD, rather suggested the aforementioned minimum data points may be collectively used as measures for CALD.

Data on spoken language is commonly used in health care research to identify vulnerable patient groups. In the health care setting, language discordance can be defined as when a patient has limited proficiency in the language spoken by their health care providers [207]. In addressing language discordance between healthcare providers and patients, as a variable for possible disparity, researchers frequently utilize data on patient's 'primary spoken language' or 'preferred spoken language' as collected by administrative staff during the hospital admission process. In studies taken place in nations where English is the predominantly spoken language, the term *limited English proficiency* (LEP) has been most commonly utilized by many researchers, where LEP denotes those patients who had a language other than English as their 'primary spoken language' [207-225]. However, other terms utilised include *language discordant*, *non-English speaking* [226], *non-English speaking background* [227], *limited English skills* [228], *non-English principal language*, [229], *patients with language barriers* and *patient-physician language concordance* [230]. And despite, the difference in terminology, the conceptual and especially operational definitions for these terms are for the most part identical. With the exception of *patient-physician language concordance* which accounts for a patient's doctor having proficiency in their primary spoken language (e.g. Spanish), which is not the principle spoken language of country (i.e. English) [230]. Studies tend not to address concepts of ethnicity and language barriers simultaneously.

2.8.3. Health disparities in CALD groups

Effective communication between healthcare providers and patients is a hallmark of good clinical practice that has shown to improve patient health [231]. Communication barriers have been identified as key contributors to adverse events in hospitals [229, 232, 233]. In the health care setting, language discordance occurs when a patient has limited proficiency in the language(s) spoken by the health care providers [207]. Numerous studies have shown language discordance negatively affects patient health outcomes [213, 217, 218, 223, 229, 232-235]. Patients with limited English proficiency have been shown to have longer hospital lengths of stay (LOS) [207, 234] increased rates of readmission [234] and unplanned

representations to hospital [236]. Studies in outpatient settings demonstrate language discordance negatively impacts patient's satisfaction and comprehension [216, 223]. A study of ambulatory HF patients, limited English proficiency (LEP) was an independent positive correlate for 18-month mortality, along with lower left ventricular ejection fraction and increased hospital utilization [237]. There are limited studies however that examine the effect of language discordance on health outcomes in disease specific patient groups.

There is a large body of evidence to indicate that racial and ethnic minority groups have disparity in health outcomes and reduced access to health care [238]. Studies in the US demonstrate that compared to white individuals, black and Hispanics people suffer disproportionately from chronic diseases [239-242], including a higher prevalence of cardiovascular disease and related risk factors [243-245]. In the UK, people of South Asian origin (Indian, Pakistani or Sri-Lankin subcontinent), who are the largest ethnic minority group in the UK (>4% of the population) have a 40% higher incidence of coronary heart disease compared to the white population [125]. In the US, compared to whites, African Americans and Latinos have a reduced ability to access to health care and lower use of non-emergency health services [246, 247]. Compared with whites, blacks and Hispanics were less likely to be adherent in cardiovascular [248, 249] and diabetes medications [250, 251], while Asians were as likely [249]. African Americans (or Blacks), have been shown to be more likely to be readmitted to the hospital following a cardiovascular related admission or major surgery compared to white patients [240, 249, 252-255]. A 2009 study which analysed US Medicare claims data of all hospitalizations from 2003-2004 identified black race to be an independent predictor of rehospitalisation [121]. In Australia, CALD populations are at an increased risk of developing chronic diseases [22] and have been shown to have increased barries to accessing health care [16, 23-25]. An Australian study, showed pregnancy outcomes are worse in CALD women compared to non-CALD women. Despite, the recognition by Australian government and health bodies of the significant health barriers for CALD communities, there is limited studies exploring health outcomes in CALD groups within Australia. In 2015 the Independent Hospital Pricing Authority (IHPA) published a costing study of CALD patients to inform a policy decision for whether an adjustment is warranted to the government healthcare pricing for CALD patients. The analysis indicated that the costs of CALD patients were not materially different from non-CALD patients at the national level, and if any disparity was present it can be accounted for lack of interpreter services where required [26]. The authors noted that there were few Australian studies and data available, which impacted on the conclusions drawn in the report.

In HF patients, North American studies have identified non-whites (blacks and Hispanics) to have longer length of stays [118, 256], as well as increased rehospitalisation rates compared to whites [117, 119, 132, 142, 144, 256-260]. These disparities persist even when controlling for the increased rate of risk factors (lower socioeconomic status and clinical co-morbidities) for HF hospitalisation, which non-whites have been shown to possess [258]. Interestingly, some studies showed that despite increased rates of short and long term readmission, mortality rates were lower in non-whites compared to whites [196, 257]. In the UK, despite major differences in incidence of coronary artery disease and baseline risk factors, there has been similar incident HF admission and readmission rates between white and South Asian patients, whereas mortality rates were lower in South Asian patients [125]. The vast majority of these studies, involve the comparator minority group comprising of one (i.e. Black, Hispanic or South Asian) or two ethnic groups (black and Hispanic) only. Whilst these studies have identified ethnicity as an important determinant of length of stay, mortality, and rehospitalisation, they did not methodically address spoken language as a potential compounding factor.

There are very few studies which investigate CALD disparities in HF patients in an Australian context [127]. One study conducted on a Melbourne HF population identified country of birth to be a predictor for 28-day readmission on a univariate analysis, however statistical significance was lost on a multivariate analysis (p=0.06) [127]. An Australian consensus statement on the approach to chronic HF care, conveyed there was lack of data and a need for more HF research into culturally and linguistically diverse populations [7].

The basis by which cultural and linguistic diversity on may impact adversely of health outcomes including rehospitalisation is undoubtedly multifactorial. Cultural differences [12, 20], communication barriers with health care providers [12, 234], poor medication adherence [13, 261], low health literacy [12, 13, 18, 262], social isolation [16, 20, 263, 264], financial constraints [18, 20, 263, 264] and discrimination [17], are just some of the factors that can contribute to disparate outcomes in these population groups. It is essential however, to first establish the existence and extent of any heath outcome disparities before we may dissect the potential mechanisms that may underpin them.

3. CHAPTER 3: The impact of cultural and linguistic diversity on rehospitalisation rates in patients with heart failure - (Study 1)

3.1. Introduction to study

3.1.1. Culturally and linguistically diversity in Australia

Australia is a culturally and linguistically diverse country. Over a quarter (26%) of Australia's 24 million population were born overseas, and of these first-generation Australians more than half (53%) speak a language other than English at home. The majority (82%) of the overseas-born population live in the capital cities, such as Melbourne, Sydney and Perth, where the proportion of overseas-born people account for one third of these cities' population [21].

Evidence demonstrates that in Australia, CALD groups suffer from poorer health and utilise health services less compared to the general population [12-14]. Limited English proficiency, cultural differences, poorer health literacy, social isolation, financial constraints and discrimination are some of the barriers that impact on the health and well-being of CALD groups [12, 13, 15, 16].

3.1.2. Western Melbourne significance

Western Melbourne is one of the fastest growing populations in Victoria, with future projected growth to be greater than 2% per annum in the next 10 years. It is home to a population with the highest proportion of CALD individuals in Victoria, with more than 37% having been born overseas, which is 11% more than the national percentage. In addition, the median individual income of households in Western Melbourne is amongst the lowest in greater Melbourne [265]. Western Health hospitals (Footscray and Sunshine Hospitals) are the principle referral hospitals in the Western Melbourne region, servicing a population of more than 800 000 people [266].

Western metropolitan Melbourne is home to some of the highest rates of HF in Victoria, compared to other government areas [267]. Western Health hospitals, which service this government area, have seen a marked increase in the number of HF hospital admissions in recent years. Data from the Western Health performance unit, showed that in 2013, there were approximately 800 HF admissions across Western Health hospitals, this number increased to 1200 in 2016 [268].

Footscray and Sunshine Hospitals are tertiary hospitals which have coronary angiography and angioplasty capabilities. These hospitals do not perform heart transplants or have capacity for mechanically assisted circulatory support. Thus, Western Health hospitals, generally do not service patients with previously have had heart transplants or whom have existing ventricular assist devices.

It is evident that Western Health services a large rapidly growing and socioeconomically disadvantaged population, with a substantial culturally and linguistically diverse representative. However, it is unclear what the effect of this diversity may have on the growing burden of HF seen in Western Melbourne and other areas.

As the burden of HF in communities is increasing, it is placing an increasing strain on hospitals and the wider healthcare system. The need to first identify possible health outcome disparities in HF patients is critical if health providers and policy makers are to take the necessary steps to address them. This study focuses on vulnerable patient groups whom are increasingly growing in Western Metropolitan Melbourne. Only through identifying and further understanding the differences in these groups can effectively changes in health-service delivery strategies and health policy be initiated.

3.2. Aims and Objectives

3.2.1. Study Aims

1. To characterise and assess the effect of cultural and linguistic diversity on hospitalisation outcomes in patients hospitalised with acute HF.
2. To utilise a novel operational definition for CALD in assessing outcomes in CALD patients and discuss its use in the context of this study.

3.2.2. Study Objectives

3.2.2.1. Primary Objective

- **Rehospitalisation.** To determine the rehospitalisation incidence and risk factors of CALD patients who are hospitalised with HF and compare these findings to patients with non-CALD patients who are hospitalised with HF.

3.2.2.2. Secondary Objectives

- **Emergency Department (ED) utilisation**. To compare ED visitation incidence in CALD and non-CALD patients.
- **Rehospitalisation.** To determine risk factors associated with increased HF rehospitalisation in the study cohort.

3.3. Methods

3.3.1. Study type and design

A retrospective observational study was performed, utilising a cohort of patients discharged with a principal diagnosis of HF from two acute metropolitan public hospitals, Footscray Hospital and Sunshine Hospital, operating as a single health network in Melbourne, Western Health.

3.3.2. Study population

The study population consists of adult patients who were hospitalised with a principle diagnosis of HF at either Footscray Hospital or Sunshine Hospital over the period of 1st of January 2013 to the 31st of July 2016.

Eligible patients were identified from hospital administrative datasets, using HF diagnostic codes based on the Australian Modified International Classification of Diseases, Tenth Revision (ICD10-AM). Patients hospitalised with a principle diagnosis of HF were identified by ICD10-AM codes (I50x, I11.0, I13.0, I13.2, I42x, I255 and J81) [175]. To minimise the potential confounding effect of frequent additional care provided to specific subgroups, patients who were identified at the time of their discharge to be dialysis-dependent or who resided permanently in a nursing home were excluded. Administrative data regarding patient rehospitalisation, emergency department (ED) visitation and mortality were retrieved for the study period, extending to a minimum of 240-days from their index HF hospitalisation. Only non-elective emergency hospitalisations and ED visitations were included: elective admissions, including dialysis, inpatient rehabilitation and transfers to subacute care were excluded. Hospitalisations that involved transfers from another health service, or that resulted in transfers to another health service were also excluded. Consistent with previous methodological

approaches with administrative datasets, non-elective admissions of less than 24 hours duration (including time spent in the ED) were excluded [269, 270]. ED visitations were defined as those presentations, which resulted in direct discharge from emergency, not resulting in transfer to a ward environment. Complete mortality data was available if death occurred within the Western Health Network or if deaths occurred in the first 30 days after any hospitalisation within the Western Health network. Beyond 30 days of a readmission, mortality data was incomplete and only available if notified by other health services.

3.3.2.1. Inclusion criteria

- Adult patients aged 18 years and older with a non-elective emergency admission to hospital, between 1st of January 2013 and the 31st of July 2016, with a principal diagnosis of HF.

3.3.2.2. Exclusion criteria

- Elective admissions.
- Admissions that result in patients leaving hospital during their treatment (i.e. transferred to another hospital or left against medical advice).
- Admissions of less than 24 hours.
- Statistical admissions (i.e. administrative record representing a change of care type within one hospital stay).
- Statistical separations.
- Dialysis dependent patients.
- Admissions from a hospital transfer.
- Admissions resulting in transfers to other hospitals.
- Admissions resulting in inpatient death.

3.3.3. Operational definitions

3.3.3.1. Heart failure operational definitions

The study cohort was identified from the Western Health Admitted Episodes dataset using HF diagnosis codes based on the Australian Modified International Classification of Diseases, Tenth Revision (ICD10-AM). Patients hospitalised with a principle diagnosis of HF were identified by ICD10-AM codes I50x, I11.0, I13.0, I13.2, I42x, I255 and J81.

The index HF admission/hospitalisation is defined as the patient's first non-elective HF admission during the 2013 to 2016 study period. All patients were be categorized as either "de novo heart failure" or as "pre-existing heart failure" based on the respective absence or presence of HF diagnoses 10 years prior to their first HF admission during the study period (i.e. the index HF admission) [39, 151, 271, 272].

The study definitions for de novo HF and pre-existing HF are as follows;

- **De novo heart failure =** If in the preceding 3 years prior to the index HF admission, the patient had no prior record of having been diagnosed with HF (principle or secondary) according to the ICD10-AM HF codes I50x, I11.0, I13.0, I13.2, I42x, I255, J81 and U822.

- **Pre-existing heart failure** = If in the preceding 3 years prior to the index HF admission, the patient was recorded as having a diagnosis of HF (principle or secondary) according to the ICD10-AM HF codes I50x, I11.0, I13.0, I13.2, I42x, I255, J81 and U822.

All HF admissions that follow the index HF admission were considered as a HF readmission/rehospitalisation.

3.3.3.2. CALD operational definitions

CALD patients were defined as those who were born outside of a principally English-speaking country and/or identified as speaking a language other than English as their primary spoken language, as recorded in hospital admission registration data. CALD patients were sub-classified as either CALD with English Proficiency (CALD-EP), based on English identified as being their primary spoken language - or as CALD with LEP (CALD-LEP), based on a documented primary spoken language being other than English. By definition, all non-CALD patients were considered to be English proficient (EP).

3.3.4. Covariate data and additional datasets

Data on covariates were obtained directly from the administrative database for sex, age at index HF admission and marital status. ICD10-AM diagnostic codes were utilized to determine clinical comorbidities at the time of the index admission. The Charlson Comorbidity Index (CCMI) was calculated as previously described [273]. A pre-existing diagnosis of HF was established for each individual in the cohort by identifying relevant ICD10-AM codes in hospital data, available from the

three calendar years prior to the study period. Where available contemporaneous echocardiographic data was obtained from hospital records. HF subtype was determined based on the reported LVEF: patients with an EF of <50% were classified as HFrEF and those with an EF of ≥50% were classified as HFpEF [31].

Socioeconomic status was determined by geospatial mapping, utilizing data from the Australian Bureau of Statistics, mapping residential addresses at the time of index admission to Statistical Area level 1 (SA1) codes [274]. SA1 codes denote small geographically defined residential areas that typically contain between 200 and 800 persons [275]. Individual SA1 codes are co-registered with Australian census data, including data relating to socioeconomic advantage and disadvantage.2011 census data, and the index of relative social advantage and disadvantage (IRSAD) was utilized as the preferred indication of socioeconomic status [276]. The IRSAD was applied to each patient based on their SA1 code and expressed in quintiles relative to the Australian population.

3.3.5. Data sources

Data for the study was derived from the following data sources:

Western Health Patient Administration System (PAS): Western Health hospitals use the i.Patient manager (i.PM), which is the most widely used PAS in public hospitals in Australia. The PAS system is episode based and contains information on patient admissions, demographic (including place of birth and spoken language), discharge diagnoses and procedures during their stay. Discharge diagnoses are recorded on the PAS by specialised coders using the ICD-10-AM. Diagnoses are based on clinical medical documentation, in particular the medical discharge summary and clinical progress notes.

Western Health Emergency Department Information System (EDIS): Western Health hospitals use EDIS, which is the most widely used emergency department patient information system in public hospitals, in Australia. Alike the PAS, EDIS contains information on patient demographics and ED visitations, including triage time, time seen by a doctor, primary diagnosis, outcome (i.e. admitted to hospital, discharge, death or left against medical advice), discharged and departure date. Discharge diagnoses are also recorded on the EDIS using the ICD-10-AM.

Western Health Admitted Episodes Dataset (AED): The AED is an episode-based system that provides comprehensive data of patient admissions. The data set includes (but not limited to); patient

demographics, times and dates of admissions and discharges, type of admission (elective or non-elective), causes of admission (diagnoses), procedures occurred, length of stay and in-hospital deaths.

Picture Archiving and Communication System (PACS) – The Western Health Cardiology Department PACS contains archived images and reports for over 15 000 echocardiogram studies. An output data set of all reports for all echocardiogram studies performed between 1st of January 2013 and 31st of December 2017 was acquired.

Socio-Economic Indexes for Areas (SEIFA): The SEIFA indexes are a widely-used measure of relative socioeconomic advantage and disadvantage in Australia. The SEIFA indexes are based geographical areas; the smallest SEIFA geographical unit is Statistical Area Level 1 (SA1). SA1 generally encompass a geographic area of 200 to 800 persons. SA1 values are assigned to individuals based on their residential address.

3.3.6. Data cleansing and linking methods

All datasets were made available in their raw form and were presented in formats standardised to the respective data source software. Thus, all raw datasets required a process of data cleansing, with all variables needing to be standardised. This allowed for effective abstraction of necessary data variables and the subsequent linkage to other datasets.

Data abstraction is the process of hiding of unnecessary data and yielding of relevant data. It often involves the removal of unwanted data, as well as the converting or translating of existing datapoints into new data points required. The process of data abstraction parallels the implementation of algorithms to operationalise study variables.

All datasets had unnecessary data points removed. Data points containing dates and/or time were standardised to a single format. All datasets have a unique identified, which all data points within the dataset referenced to. The unique identifiers were as follows; episode number for AED, episode number for EDIS, study ID for PACS, patient UR number for iPM, subject ID for SEIFA, and subject ID for the baseline study cohort (once identified). All datasets were than referenced and linked to the subject ID of the identified baseline study cohort.

Admission episodes datasets were cleansed of admitted episodes data that do not fulfil the inclusion criteria or meet the exclusion criteria. Total inpatient length of stay were determined by the addition

of the ED length of stay from EDIS, to the inpatient length of stay from the AED. Inpatient admitted episodes of <24 hours were not considered as a hospitalisation as per the operational definition previously described. Inpatient admitted episodes of <24 hours were instead classified as only an ED visitation.

The identification of index HF admissions as well as days from index HF admission to next subsequent readmissions had been performed using PowerPivot in Microsoft Excel [277]. Examples of PowerPivot formulas to abstract these data are provided in the appendix (appendix 7.2).

Clinical co-morbidities and Charlson co-morbidity index were identified from ICD-10-AM codes and converted to single data points (see appendix 7.3).

Data linkage was be performed using a deterministic approach[278] using the unique identifiers (outlined above). At each linkage a manual review of 50 random matches was performed to validate the linkage process.

3.3.7. Sample size calculation

The choice of whether to adopt a one-sided or two-sided power calculation sample size estimation was decided on logical grounds not statistical ones [279]. A one-sided power calculation was used in this study context, since ethnicity or LEP status has not previously been found to be associated with beneficial health outcomes (including rehospitalisation) in various study populations (as discussed in Chapter 2, section 2.8.3). A two-sided statistical approach was not adopted as it requires an increase in sample size to achieve the same statistical power, with no logically foreseeable benefit for this study.

With 500 CALD-LEP patients and 1000 EP patients (the proportions expected in a Western Health population) [268], there will be an 84% chance of detecting a significant difference at a one-sided 0.05 significance level [280]. This assumes a 30% excess (effect size) of incident rehospitalisation in the CALD-LEP group at 180 days (a conservative average effect size derived from reports documenting differential readmission rates, as discussed is Chapter 2, section 2.5.4), versus the expected baseline rate of this outcome i.e. 18% readmission at 180 days [116].

3.3.8. Statistical analysis

Between-group differences in categorical variables were assessed with the Chi squared test. Survival methodology was used to investigate differences in time to first event between non-CALD, CALD-EP and CALD-LEP groups. Separate analyses for time to first HF-related non-elective hospital readmission (HF rehospitalisation), all-cause non-elective hospital readmission (all-cause rehospitalisation), as well as time to first ED visitation was performed. For all analyses, patients were censored at the end of follow-up or if recorded as deceased. Univariate analyses were performed using the non-parametric Kaplan-Meier and the log-rank test and ties in failure times were handled using Efron's method. To adjust for a potential confounding, Cox proportional hazard model was utilized, including the following covariates: age, sex, indicator variables for pre-existing HF, chronic kidney disease, hypertension, ischaemic heart disease, sleep apnoea, stroke, diabetes, obstructive lung disease, dementia, history of malignancy, marital status and IRSAD score. All analyses were performed using the R software (R 3.4.2) [(281)].

3.3.9. Ethics

Low risk ethics approval was obtained from the Western Health Office of Research in 2016.

3.4. Results

3.4.1. Study population characteristics

In the 2013-2016 period, a total of 1613 patients were identified with an index non-elective admission in which HF was recorded as the principle diagnosis [mean age 79±6 (SD) years; 51% male]. The mean CCI was 5.5 and the two most prevalent comorbidities were hypertension (80%) and atrial fibrillation (53%). Echocardiogram data was available on 1005 patients (63%) and of these patients the prevalence of HFpEF was 52%.

There were 82 different countries of birth identified in the cohort. Of these 10 were principally English-speaking countries. The most represented countries were Australia (30%), Italy (12%), Malta (9%), Greece (6%), Macedonia (5%), Croatia (4%), England (3%), Vietnam (3%) and Poland (3%). A total of

40 different primary spoken languages were identified in the cohort, the most common were English (66%), Italian (8%), Greek (6%), Macedonian (4%), Croatian (3%) and Vietnamese (2%) (see Table 3.41). In terms of pre-specified CALD groupings, the HF cohort was divided approximately into thirds: 36% were classified as non-CALD, 30% were CALD-EP and 34% were CALD-LEP, as shown in Table 3.41. CALD-LEP patients tended to be older at index admission and more likely to be female. The CALD-LEP group had higher proportions of pre-existing HF, atrial fibrillation, hypertension, chronic kidney disease, stroke and dementia. In contrast, the CALD-EP group exhibited the highest proportion of ischaemic heart disease. The average length of in-hospital stay was 5 days and did not differ significantly between the three groups. In terms of socioeconomic status, 41% (662) of patients were in the lowest SA1 quintile, with a high proportion of CALD patients (CALD-EP and CALD-LEP) in the lowest SES quintile.

Table 3.41: Study population baseline characteristics

	All patients (n=1613)	Non-CALD (n=583)	CALD-EP (n=488)	CALD-LEP (n=542)	P-value
Age (mean, SD)	77 (12)	75 (14)	76 (12)	80 (8)	<0.001
Age groups (n, %)					<0.001
0-64 years	224 (14)	126 (22)	72 (15)	26 (5)	
65-74 years	330 (20)	123 (21)	127 (26)	80 (15)	
75-84 years	611 (38)	178 (31)	171 (35)	262 (48)	
>84 years	448 (28)	156 (27)	118 (24)	174 (32)	
Gender (n, %)					0.001
Male	825 (51)	287 (49)	284 (58)	254 (47)	
Female	788 (49)	296 (51)	204 (42)	288 (53)	
Marital status (n, %)					<0.001
Single or widowed	654 (41)	250 (43)	172 (35)	232 (43)	
Married or de-facto	835 (52)	264 (45)	280 (57)	291 (54)	
Separated or divorced	111 (7)	57 (10)	36 (7)	18 (3)	
Not stated	13 (1)	12 (2)	0 (0)	1 (0)	
Socioeconomic status SA1 (n, %)					0.003
1st Quintile	662 (41)	213 (37)	218 (45)	231 (43)	
2nd Quintile	446 (28)	164 (28)	125 (26)	157 (29)	
3rd Quintile	268 (17)	114 (20)	80 (16)	74 (14)	
4th Quintile	173 (11)	60 (10)	44 (9)	69 (13)	
5th Quintile	61 (4)	31 (5)	19 (4)	11 (2)	
Country of birth (n, %)					<0.001
Australia	481 (30)	477 (82)	0	4 (1)	
Italy	189 (12)	-	73 (15)	116 (21)	
Malta	153 (9)	-	125 (26)	28 (5)	
Greece	100 (6)	-	19 (4)	81 (15)	
Macedonia	76 (5)	-	14 (3)	62 (11)	
Croatia	70 (4)	-	24 (5)	46 (8)	
England	48 (3)	48 (8)	0 (0)	0 (0)	
Vietnam	44 (3)	-	5 (1)	39 (7)	
Poland	43 (3)	-	26 (5)	17 (3)	
Other	409 (25)	58 (10)	202 (41)	149 (27)	
Primary spoken language (n, %)					<0.001
English	1071 (66)	583 (36)	488 (30)	0	
Italian	121 (8)	-	-	121 (22)	
Greek	94 (6)	-	-	94 (17)	
Macedonian	64 (4)	-	-	64 (12)	
Croatian	47 (3)	-	-	47 (9)	
Vietnamese	32 (2)	-	-	32 (6)	
Maltese	31 (2)	-	-	31 (6)	
Arabic	22 (1)	-	-	22 (4)	
Polish	16 (1)	-	-	16 (3)	
Other	115 (7)	-	-	115 (21)	
Heart failure type (n, %)					0.190
HFrEF	489 (30)	176 (30)	159 (33)	154 (28)	
HFpEF	534 (33)	169 (29)	170 (35)	195 (36)	
Unavailable	590 (37)	238 (41)	159 (33)	193 (36)	
Comorbidities (n, %)					
History of alcohol abuse	95 (6)	40 (6)	31 (6)	24 (4)	0.190
Atrial fibrillation	862 (53)	293 (50)	255 (52)	314 (58)	0.029
Chronic kidney disease	814 (50)	257 (44)	244 (50)	313 (58)	<0.001
Hypertension	1288 (80)	437 (75)	386 (79)	465 (86)	<0.001
Prior history of heart failure	657 (41)	205 (35)	191 (39)	261 (48)	<0.001
Ischaemic heart disease	947 (59)	305 (52)	316 (65)	326 (60)	<0.001
Obesity	264 (16)	113 (19)	74 (15)	77 (14)	0.047
History of VTE	144 (9)	58 (10)	40 (8)	46 (8)	0.560
Sleep apnoea	186 (12)	66 (11)	61 (13)	59 (11)	0.707
Stroke	242 (15)	70 (12)	72 (15)	100 (18)	0.010
Diabetes	839 (52)	256 (44)	272 (56)	311 (57)	<0.001
Obstructive lung disease	737 (46)	261 (45)	229 (47)	247 (46)	0.631
History of malignancy	285 (18)	98 (17)	91 (19)	96 (18)	0.735
Dementia	173 (11)	46 (8)	39 (8)	88 (16)	<0.001
Charlson Comorbidity Index (mean, SD)	5.5 (3.3)	5.0 (3.4)	5.6 (3.1)	6.0 (3.3)	<0.001

For those patients for whom HF subtype was known (63%), HF type was not associated with CALD grouping, or with rehospitalisation or emergency visitation rates. As there was no association of HF type on a univariate analysis and availability of echocardiographic information was incomplete across the patient sample, this variable was not included in the multivariate analysis.

3.4.2. Readmission outcomes and survival analyses

Readmission rates at 30, 180 and 365 days are presented for each group in Table 3.42. At 30 days, the rate of all-cause rehospitalisation for the overall cohort was 17.2%. The observed pattern on the fitted Kaplan-Meier curves was consistent for HF-related readmission, all-cause readmission and ED visitation (see Figure 3.4). CALD-LEP patients tended to have rehospitalisation sooner than non-CALD patients, whereas CALD-EP rehospitalisation rates tended to be intermediate and fall between the CALD-LEP and non-CALD groups. Given that this finding was broadly consistent with the relative distribution of increased age and co-morbidities among the three groups, a Cox proportional hazards model was subsequently fit to adjust for potential confounding. Adjusted and unadjusted hazard ratios are displayed in Table 3.43. While adjustment decreases the size of the effect, evidence of an independent effect of CALD grouping remained for HF-related readmission. Estimates of the hazard ratios for confounding variables for HF-related rehospitalisation are displayed in Table 3.44.

Table 3.42: Cumulative incidence rates and 95% confidence intervals for rehospitalisation and emergency department visitation at specific times after discharge from the index admission

	All patients (n=1613)	Non-CALD (n=583)	CALD-EP (n=488)	CALD-LEP (n=542)
ED visitation				
30 days	7.7% (5.4 - 9.9%)	6.2% (4.2 - 8.2%)	8.0% (5.6 - 10.4%)	8.7% (6.3 - 11.1%)
180 days	28.7% (24.7 - 32.5%)	23.3% (19.7 - 26.8%)	27.9% (23.7 - 31.8%)	34.8% (30.5 - 38.7%)
365 days	41.6% (37.1 - 45.8%)	33.8% (29.6 - 37.8%)	42.1% (37.4 - 46.5%)	48.9% (44.3 - 53.1%)
All-cause readmission				
30 days	17.3% (14 - 20.5%)	16.6% (13.5 - 19.5%)	16.3% (12.9 - 19.5%)	19.1% (15.7 - 22.4%)
180 days	41.9% (37.6 - 46%)	39.2% (35.1 - 43.1%)	40.1% (35.5 - 44.3%)	46.5% (42.1 - 50.6%)
365 days	55.6% (51.1 - 59.7%)	50.2% (45.8 - 54.2%)	54.8% (50 - 59.1%)	61.8% (57.4 - 65.7%)
HF-related readmission				
30 days	8.6% (6.2 - 11%)	7.3% (5.1 - 9.4%)	7.9% (5.4 - 10.2%)	10.8% (8.1 - 13.4%)
180 days	20.3% (16.8 - 23.7%)	17.1% (13.9 - 20.1%)	18.3% (14.7 - 21.7%)	25.7% (21.8 - 29.3%)
365 days	27.3% (23.3 - 31.1%)	21.6% (18.1 - 25%)	26.2% (22 - 30.1%)	34.2% (29.9 - 38.1%)

Abbreviations: CALD, non-culturally and linguistically diverse patients; CALD, culturally and linguistically diverse patients; CALD-EP, culturally and linguistically diverse patients with English proficiency; CALD-LEP, culturally and linguistically diverse patients with limited English proficiency; ED, emergency department; HF, heart failure.

Apart from CALD-LEP, covariates independently associated with HF-related readmission in this cohort included atrial fibrillation, chronic kidney disease, obstructive lung disease, pre-existing HF diagnosis, ischaemic heart disease and sleep apnoea. Conversely, the presence of diabetes and a history of malignancy appeared to predict reduced HF-related readmission.

Overall mortality rate at 30 days and 365 days, where 1.7% and 17% respectively. There were no significant between group differences in unadjusted mortality rate at 30 days (p=0.5) and 365 days (p=0.12).

Table 3.43: Univariate and multivariate associations for rehospitalisation and emergency department visitation, using three CALD classification models.

	Non-CALD	CALD-EP	CALD-LEP	Non-CALD	CALD (CALD-EP + CALD-LEP)	EP (Non-CALD + CALD-EP)	CALD-LEP
ED visitation							
Unadjusted	ref	1.23* [1.03; 1.47]	1.52* [1.29; 1.79]	ref	1.38* [1.19; 1.60]	ref	1.37* [1.20; 1.58]
Adjusted	-	1.15 [0.96; 1.38]	1.40* [1.18; 1.67]	-	1.28* [1.09; 1.49]	-	1.30* [1.13; 1.51]
All-cause readmission							
Unadjusted	ref	1.10 [0.94; 1.28]	1.38* [1.19; 1.59]	ref	1.24* [1.09; 1.41]	ref	1.32* [1.16; 1.49]
Adjusted	-	0.93 [0.79; 1.09]	1.03 [0.88; 1.20]	-	0.98 [0.86; 1.12]	-	1.07 [0.94; 1.22]
HF-related readmission							
Unadjusted	ref	1.21 [0.97; 1.51]	1.64* [1.34; 2.02]	ref	1.43* [1.19; 1.73]	ref	1.50* [1.26; 1.78]
Adjusted	-	1.04 [0.83; 1.30]	1.27* [1.02; 1.57]	-	1.15 [0.95; 1.40]	-	1.24* [1.04; 1.49]

* denotes statistical significance. Hazard Ratio's (HR) and 95% Confidence Intervals (CI) are estimated by Cox proportional hazard model, with and without adjustment for covariates of age, gender, marital status, SA1 quintile, atrial fibrillation, chronic kidney disease, hypertension, history of heart failure, ischaemic heart disease, sleep apnoea, stroke, diabetes, obstructive lung disease, history of malignancy, dementia and Charlson co-morbidity index.

Abbreviations: non-CALD, non-culturally and linguistically diverse patients; CALD, culturally and linguistically diverse patients; CALD-EP, culturally and linguistically diverse patients with English proficiency; CALD-LEP, culturally and linguistically diverse patients with limited English proficiency; EP, English proficient patients (includes non-CALD and CALD-EP); ED, emergency department; ED, emergency department; HF, heart failure.

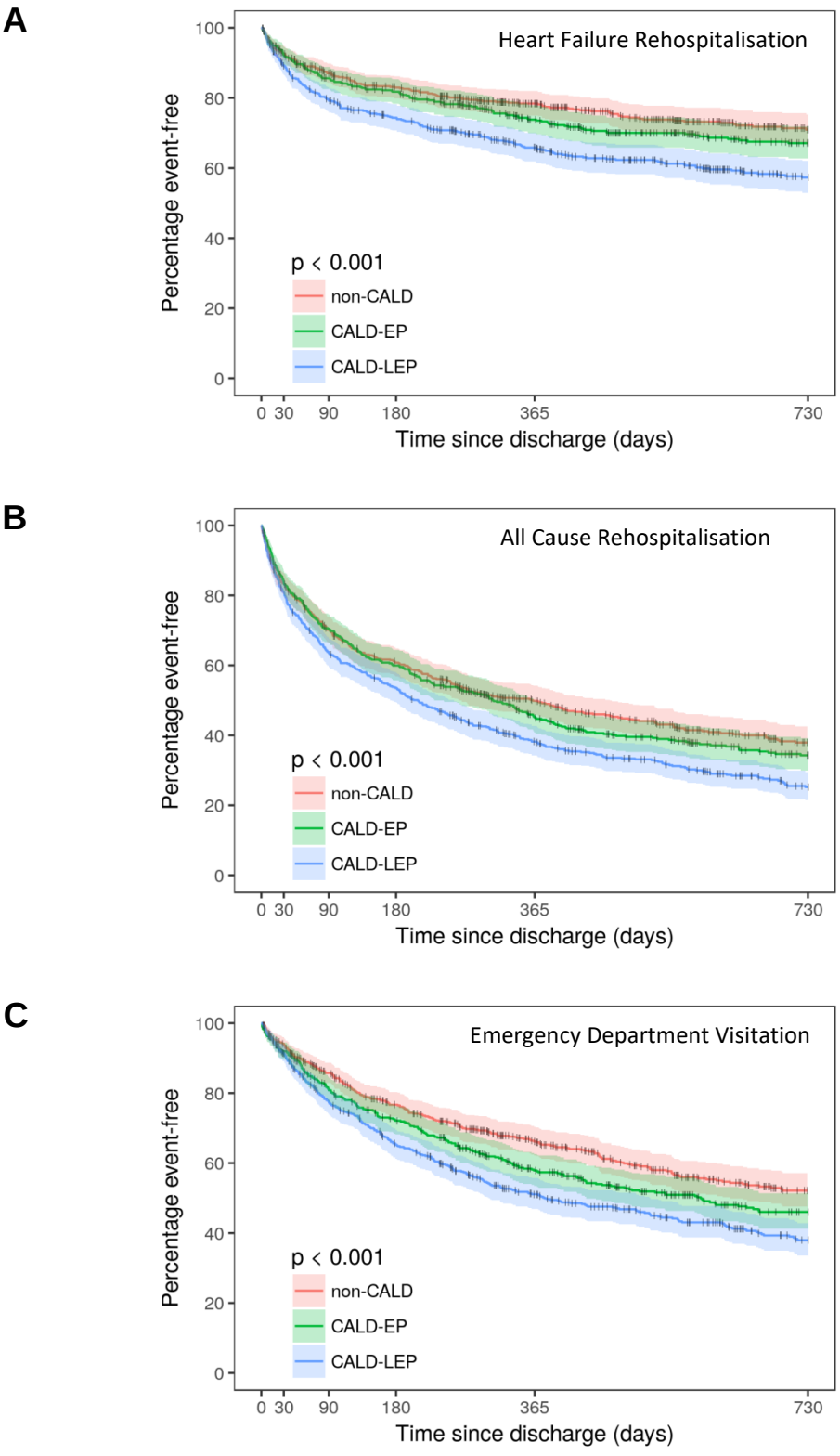

Figure 3.4: Fitted Kaplan-Meier curves for (A) heart failure rehospitalisation, (B), all-cause rehospitalisation and (C) emergency department visitation. The observed pattern is consistent for emergency department visitation and rehospitalisation and in both heart failure related and all-cause rehospitalisation. CALD-LEP patients represent sooner than non-CALD patients and the rates CALD-EP rates are in-between.

Table 3.44: Predictors for heart failure rehospitalisation in the multivariate survival analysis

Variables	Hazard Ratio	95% Confidence Interval	P-value
CALD-Group			
Non-CALD	ref		
CALD-EP	1.04	0.82 - 1.30	0.76
CALD-LEP	1.27	1.02 - 1.57	0.03
Age groups			
0-64	ref		
65-74	1.04	0.74 - 1.47	0.81
75-84	1.11	0.80 - 1.54	0.53
85+ over	1.22	0.86 - 1.74	0.27
Gender			
Female	1.12	0.93 - 1.34	0.24
Male	ref		
Marital status			
Single or widowed, Separated or	ref		
Married or de-facto	1.01	0.84 - 1.22	0.90
Socioeconomic status (SA1 Quintiles)			
1st Quintile	ref		
2nd Quintile	0.97	0.78 - 1.20	0.79
3rd Quintile	1.13	0.89 - 1.44	0.31
4th Quintile	1.18	0.89 - 1.57	0.26
5th Quintile	0.75	0.41 - 1.34	0.33
Comorbidities			
History of alcohol abuse	0.77	0.49 - 1.19	0.24
Obstructive lung disease	1.27	1.06 - 1.52	0.01
Atrial fibrillation	1.57	1.31 - 1.89	<0.001
Chronic kidney disease	1.89	1.48 - 2.42	<0.001
Hypertension	1.16	0.85 - 1.57	0.35
History of heart failure	1.23	1.03 - 1.46	0.02
Ischaemic heart disease	1.37	1.12 - 1.69	<0.01
History of thromboembolism	1.1	0.83 - 1.46	0.52
Sleep apnoea	1.62	1.27 - 2.06	<0.001
Stroke	0.96	0.75 - 1.23	0.76
Diabetes	0.72	0.56 - 0.93	0.01*
History of malignancy	0.69	0.53 - 0.89	0.01*
Dementia	0.82	0.63 - 1.08	0.16
Charlson co-morbidity Index			
0 - 2	ref		
3 - 4	1.34	0.91 - 1.97	0.14
5 - 6	1.73	1.12 - 2.68	<0.01
7 - 8	2.19	1.32 - 3.65	<0.01
9 +	2.35	1.33 - 4.17	<0.01

* factors were associated with statistically significant reduced readmission, rather than increased readmission.

3.5. Discussion

In the context of a multicultural metropolitan health service, this study demonstrates a graduated risk of HF rehospitalisation associated with CALD grouping. An increased incidence of HF-related readmission and ED visitation was observed in CALD-LEP patients when compared to non-CALD patients. This association persisted after multivariable adjustment for comorbidities and socioeconomic status. The CALD-EP group appeared to carry an intermediate risk, exhibiting (non-statistically significant) trends towards earlier rehospitalisation and ED visitation, when compared to their non-CALD counterparts.

This study adds to the body of evidence that has shown language discordance [207] and ethnicity are proxies for adverse health outcomes in HF and other medical populations [229, 232, 282]. Few studies, have sought to address ethnic diversity and language discordance concurrently, specifically in a HF population. CALD status, based primarily on country of birth (nativity) is operationally equivalent to the designation of ethnic minorities used in other studies [283-288]. Likewise, the CALD subgroup (i.e. CALD-LEP) based on identifier of primary spoken language is operationally comparable to studies investigating minority groups with language discordance [207, 209, 218, 282, 289] and for low acculturation [143]. Our use of a novel framework for the operational definitions for CALD and CALD subgroups (CALD-EP and CALD-LEP) was intended to better represent the continuum of diversity and disparity in the CALD population and to help ascertain if patient outcomes change along this continuum. The CALD-LEP subgroup likely represents one end of the continuum of diversity, at which there exists a greater potential for lack of acculturation, in addition to a potential language barrier, both of which have health disparity implications. By contrast, CALD-EP likely denotes less risk of a barrier to communication, but with a variable component of acculturation. The fact that these designations appeared to capture the extent of clinical risk, in this case indexed by HF rehospitalisation, while not validating this framework entirely, lends support to it.

Nativity and language discordance are but two identifiers for a complex heterogenous group of patients. The nature and direction of the relationship between these identifiers and the concept of cultural and linguistic diversity cannot be assumed to be orthogonal. To this effect, the assumption does not hold that the health disparity in the CALD population will change commensurately to variations of the identifying variables. For example; if a cohort of CALD-LEP patients became proficient in English, this would not confer a commensurate improvement in their health status. English proficiency is likely associated also with other variables, latent or otherwise, that were not included in

this study; variables that may be difficult to record or even define, such as health literacy and acculturation. While interventions focused on improving communication between patient and health care provider may capture causal effects (e.g. improved medication adherence through better communication), they may not concomitantly address the pathways from other potential influences – such as acculturation, socioeconomic status, health literacy, stigma and cultural beliefs. This in mind, health strategies aimed to address health disparity in CALD populations undoubtedly will require a multipronged approach, rather than one focussed exclusively on language.

Capturing the multidimensional nature of CALD populations by using any one or several measures is inherently challenging. In many research settings, there are limited variables which can be practicably utilized to represent the spectrum and heterogeneity of CALD patients. In the case of administrative health data sets, the collected information is largely pragmatic and categorical, without a focus on qualitative measures. Future studies, may incorporate the use of multiple categorical and continuous measures (e.g. time since migration and level of English proficiency), which look to better characterise the dimensionality and continuum of diversity in CALD populations. Such research could augment the interpretations drawn on the basis of studies that have utilized any single or multiple categorical indicators.

In understanding the findings of this study, numerous potential mechanisms for these differences can be discussed. Poor communication between patients, their families and health care providers may result in suboptimal medical treatment, or even where medical treatment is optimal, poor understanding may result in inappropriate presentation to a health care organisation. This may further be compounded where there are coexistent low health literacy, social isolation and/or cultural barriers, all of which are known to adversely impact CALD groups [12, 14-16]. HF is associated with intermittent decompensation and serial readmission, in which outcomes are enhanced by interdisciplinary systems of care [57] and patient education [290], and negatively associated with lower socioeconomic status [138]. Whilst socioeconomic status was indexed, reduced variation in the cohort may have resulted in limited statistical power, given that the majority were in the lowest two quintiles. Disparities in educational level and health literacy, in addition to variation in health care beliefs and behaviours, may interact with CALD status and were not completely controlled for in our patient sample. The CALD group in this study cohort were represented by 75 different countries of origin and 40 different languages. This very heterogenous group, is in contrast to the homogeneity of non-CALD patients, which comprise of individuals predominantly of whom are of Anglo-Celtic ancestry [291]. Thus,

it is not possible to exclude biological differences that may have contributed to the between group differences observed.

The clinical characteristics of the cohort in this study is similar to that of contemporary HF studies in terms of multimorbidity and proportion of HFpEF and HFrEF [292, 293]. In this study, clinical comorbidities associated with early rehospitalisation included chronic kidney disease, atrial fibrillation, ischaemic heart disease, sleep apnoea, obstructive lung disease and hypertension, which are in keeping with previous studies [294, 295]. The proportion of HF subtypes were equally represented and neither were associated with differential risk of rehospitalisation.

Two specific observations in this study require comment. A negative association was found between diabetes and readmission, which is in contrast to other studies [296]. Since the presence of diabetes contributes to ischaemic heart disease and chronic kidney disease, both of which were positive predictors in the multivariate model, it is postulated that the adjusted group represents relatively uncomplicated or well-controlled diabetics. Malignancy was also negatively associated with readmission. This finding may be misleading, as planned or elective admissions, which include chemotherapy treatments, were excluded from analyses.

Our study has the expected limitations of observational research based on administrative data. This study was confined to broad definitions of the culture and language groups studied, which are unlikely to fully capture the capacities of individual patients in regards to communication, self-care and accessing of health care services - for which prospective qualitative studies would be necessary. Whereas it is intuitive that poorer outcomes will be observed in CALD groups, the extent to which it may interact with health literacy and other social determinants of health needs to be elucidated. A key limitation is the absence of complete long-term mortality outcomes, whilst complete mortality data was available for the first 30 days, death status was only available beyond 30 days if the individual died as an inpatient in the hospital network or if notified by other health services. As a result, some uncaptured deaths that occurred beyond 30 days out of hospital were not censored in the survival analysis.

Of note, the use of interpreter services in the care of CALD patients in this cohort was not determined. Furthermore, it cannot be excluded that an excess of ED visitations in CALD patients in part reflects health care beliefs and/or barriers to access, favouring use of a hospital ED over consultation with a local medical officer/general practitioner. Finally, our study cohort did not include indigenous patients

in significant numbers and cannot address the effect of indigenous status on outcomes in this disease context.

4. CHAPTER 4: A comparison of measures of rehospitalisation burden in heart failure with reduced versus preserved ejection fraction - (Study 2)

4.1. Introduction to study

Worldwide HF is a leading cause of morbidity and mortality, and is associated with a high burden of rehospitalisation. Traditionally, a "first-event" event approach has been the method used to evaluate the risk of adverse events in HF, including the risk of rehospitalisation. However, first event methods ignore all the subsequent outcomes occurring after the first event. The analysis of repeated hospitalisations or recurrent events can yield clinical insights that would be missed in an evaluation of first events only [(297)]. In HF patients the analysis of all recurrent events may be a more reflective measure of the true burden of disease. The importance and value of measuring recurrent hospitalisations or recurrent events in HF studies has been discussed in the thesis introduction (section 1.74). However, despite this promise, recurrent event analysis remains an infrequently used index in studies of HF natural history or therapeutic interventions in this group.

The aim of this study was primarily methodological, in that we sought to explore the differential or perhaps divergent characteristics and capabilities of competing statistical approaches. To do this, we took advantage of a basic subclassification applied to clinical HF syndromes, namely HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF) (discussed in introductory chapter). These subtypes were selected in part because studies to date have shown that the risk of rehospitalisation following an acute HF admission is comparable between HFrEF and HFpEF groups, in both the short and long terms [(298, 299)].

Hence, we sought to compare the burden of rehospitalisation over time in patients with HF according to subtype (HFpEF versus HFrEF), using three statistical approaches, including a recurrent event analysis. Based on literature, a null hypothesis was nominated - that there would not be between-group difference in rates of readmission, either HF-related readmission or all cause readmission.

4.2. Aims

4.2.1. Study Aims

1. To characterize the burden of rehospitalisation over time in patients with HF according to subtype (HFpEF vs HFrEF), using three different statistical approaches, including a novel recurrent event analysis.
2. To compare the results of each these statistical approaches as a measure of rehospitalisation burden.

4.3. Methods

4.3.1. Study design and study population

A retrospective observational study was performed, utilising a cohort of patients discharged with a principal diagnosis of HF from two acute metropolitan public hospitals, Footscray Hospital and Sunshine Hospital, operating as a single health network in Melbourne, Western Health. The study period was from the 1st of January 2013 to the 31st of December, 2017. Eligible patients were identified from hospital administrative datasets, using HF diagnostic codes based on ICD10-AM. Patients hospitalised with a principle diagnosis of HF were identified by ICD10-AM codes (I50x, I11.0, I13.0, I13.2, I42x, I255 and J81) [175]. Only patients with information on left ventricular ejection fraction were included. To minimise the potential confounding effect of frequent additional care provided to specific subgroups, patients were excluded who were identified at the time of their discharge to be dialysis-dependent or who resided permanently in a nursing home.

Administrative data regarding patient rehospitalisation, ED visitation and mortality were retrieved for the study period, extending to a minimum of 30-days from their index HF hospitalisation. Only non-elective emergency hospitalisations were included: elective admissions, including dialysis, inpatient rehabilitation and transfers to subacute care were excluded. Hospitalisations that involved transfers from another health service, or that resulted in transfers to another health service were also excluded. Consistent with previous methodological approaches with administrative datasets, non-elective admissions of less than 24 hours duration (including time spent in the ED) were excluded [269, 270]. ED

visitations were defined as those presentations which resulted in direct discharge from emergency. An analysis of ED visitations was not performed in this study. Complete mortality data was available if death occurred within the Western Health Network or if deaths were notified by other health services.

4.3.2. Study definitions and heart failure subgroup classification

According to the study aims, all patients were placed into two subgroups, HFrEF or HFpEF, based on (i) administrative data confirming a clinical episode of HF requiring within hospital treatment and (ii) imaging data or prior documentation in medical records designating either reduced or preserved ejection fraction. Since the imaging data sources available were varied, a hierarchical approach was adopted, as follows:

Echocardiographic data. Where available, data from the echocardiogram performed closest to the patient's index HF admission was utilised. Patients were designated HFpEF if they had had either an EF of ≥50%, or if the calculated EF was not documented, the left ventricular systolic function was described as Normal or Preserved. Patients were designated HFrEF if they had had either an EF of<50%, or if the calculated EF was not documented, the left ventricular systolic function was described as reduced [(31)].

Cardiac magnetic resonance imaging (cMRI). In patients without echocardiographic data available and where available, data from a cMRI performed closest to the patient's index HF admission was utilised. The process for designating HF subtype was carried out the same as for echocardiographic data.

Myocardial perfusion imaging via nuclear scintigraphy. In patients without echocardiographic or cMRI data available and where available, data from a nuclear myocardial perfusion imaging study that was performed closest to the patient's index HF admission was utilised. The process for designating HF subtype was carried out the same as for echocardiographic data.

Angiography. In patients without echocardiographic, cMRI or nuclear myocardial perfusion imaging study data available and where available, data from left ventriculography performed during coronary angiography was utilised. The study performed closest to the patient's index HF admission was used. The process for designating HF subtype was carried out the same as for echocardiographic data.

Medical documentation. In patients without imaging data available, HF subtype was ascertained from the medical records. Patients were designated as HFpEF if there was documentation in the notes that described the patient as having a normal or preserved left ventricular systolic function or an EF ≥50% based on external imaging which was unavailable to the study investigators. Conversely, patients were designated as HFrEF if there was documentation in the medical record that described the patient as having reduced left ventricular systolic function or an EF of <50%.

4.3.3. Covariate data and additional datasets

Data on covariates were obtained directly from the administrative database for sex, age at index HF admission and marital status. ICD10-AM diagnostic codes were utilised to determine clinical comorbidities at the time of the index admission. The Charlson Comorbidity Index (CCMI) was calculated as previously described [273]. A pre-existing diagnosis of HF was established for each individual in the cohort by identifying relevant ICD10-AM codes in hospital data, available from the three calendar years prior to the study period. Where available contemporaneous echocardiographic data was obtained from hospital records.

4.3.4. Data sources, sample size and linking methods

Data sources are the same as previously described in chapter 3 (section 3.3.6), expect where additional data on EF was attained (described above).

The study builds upon the methodology utilised in chapter 3, including estimated sample size. During the study in Chapter 3, it was revealed that a significant proportion of patients identified with a HF admission do not have corresponding data on ejection fraction (approximately one third). In light of this and to improve the power for each statistical approach, the maximal number of patients who had available data at the time the study had been embarked upon were investigated. In addition, with the adoption of different statistical approaches, the follow-up period was reduced to a minimum of 30 days as opposed to 180 days. Consequently, the study period in which subjects were identified was 18 months greater than what was carried out in chapter 3.

Data cleansing and linking methods were performed as previously described in chapter 3.

4.3.5. Statistical analyses

Between-group differences in categorical variables were assessed with the Chi squared test. When comparing each of the three models, in keeping with our hypothesis stated in null form, a primary comparison was over a 12-month period. A logistic regression analysis for 30 and 365-day HF, All Cause and Non-HF rehospitalisation rate was utilised. Survival methodology was used to investigate differences in time to first event HFpEF and HFrEF groups. Separate analyses were performed for time to first HF-related non-elective readmission, non-HF related non-elective readmission and all-cause non-elective readmissions, as well as time to first ED visitation. For all analyses, patients were censored at the end of follow-up or if recorded as deceased. Univariate analyses were performed using the non-parametric Kaplan-Meier and the log-rank test and ties in failure times were handled using Efron's method. To adjust for a potential confounding, Cox proportional hazard model was utilised, including the following covariates: age, sex, indicator variables for pre-existing HF, chronic kidney disease, hypertension, ischaemic heart disease, sleep apnoea, stroke, diabetes, chronic obstructive airways disease, dementia, history of malignancy, marital status. All analyses were performed using the R software (R 3.4.2) [(281)]. Finally, a Negative Binomial model was utilised for the assessment of recurrent event rate, as expressed as the event rate ratio.

4.4. Results

4.4.1. Study population characteristics

In the 2013-2017 period, a total of 1881 patients were identified with an index non-elective admission in which HF was recorded as the principle diagnosis [mean age 74±12 (SD) years; 53% male]. The mean CCMI was 5.5 and the two most prevalent comorbidities were hypertension (83%), ischaemic heart disease (63%), diabetes (53%) and atrial fibrillation (52%). The prevalence of HFpEF was 52%. The study population baseline characteristics are presented in Table 4.31. The HFpEF group, were older, more likely to be female and be single or divorced or widowed. HFpEF patients had more comorbidities as demonstrated by greater number of patients with a CCMI of 8 of greater. The HFpEF group had higher proportions atrial fibrillation, hypertension, obstructive lung disease, stroke and sleep apnoea. On the other hand, the HFrEF group had higher proportions of ischaemic heart disease. There was no statistically significant between group differences demonstrated in the percentage of patients with history of prior HF, chronic kidney disease, diabetes or dementia, however there tended to be a trend towards increase proportions of these conditions in the HFpEF group.

The overall mean LOS per readmission of any type was 5.71 days. For all-cause, HF related and non-HF related readmissions the mean LOS (in days) for HFpEF and HFrEF groups were; 5.89 vs 5.48 ($p<0.001$), 5.39 vs 5.34 ($p=0.96$), 6.13 vs 5.58 ($p=0.004$), respectively. The statistically significant increase seen in HFpEF mean LOS for readmission of any cause, appears to be driven by the increased mean LOS of non-HF related readmissions in this group. There was no statistically significant difference seen in the mean LOS for HF related readmissions between groups.

Table 4.31: Study population baseline characteristics

	HFpEF	HFrEF	P-value
Count (Total = 1881)	n= 971 (52%)	n= 910 (48%)	
Age (mean, sd)	77 (10.7)	72.8 (13.6)	p<0.001
Gender (n, %)			
Female	567 (58.4%)	324 (35.6%)	p<0.001
Marital Status (n, %)			
Single/Divorced/Widowed	479 (49.5%)	392 (43.4%)	p<0.001
Comorbidities (n, %)			
Prior Heart Failure	321 (33.1%)	285 (31.3%)	p=0.42
Atrial fibrillation	545 (56.1%)	440 (48.4%)	p<0.001
Hypertension	833 (85.8%)	729 (80.1%)	p=0.001
Ischaemic heart disease	593 (61.1%)	645 (70.9%)	p<0.001
Obstructive lung disease	464 (47.8%)	372 (40.9%)	p=0.003
Chronic kidney disease	501 (51.6%)	438 (48.1%)	p=0.13
Stroke	172 (17.7%)	118 (13%)	p=0.004
Diabetes	526 (54.2%)	468 (51.4%)	p=0.23
Sleep apnoea	139 (14.3%)	79 (8.7%)	p<0.001
Dementia	111 (11.4%)	74 (8.1%)	p=0.16
Charlson Comorbidity Index (n, %)			
[0-2]	191 (19.7%)	226 (24.8%)	p=0.007
[2-4]	198 (20.4%)	197 (21.6%)	p=0.51
[4-6]	212 (21.8%)	188 (20.7%)	p=0.53
[6-8]	186 (19.2%)	154 (16.9%)	p=0.21
[8 +]	184 (18.9%)	145 (15.9%)	p=0.03

Abbreviations: HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

4.4.2. Readmission outcomes

The frequency of hospital readmissions, as well as the readmission rates (at 30 and 365 days) and event rates for HFpEF and HFrEF groups are presented in Table 4.32. Overall, there were 6597 readmissions in total over the course of the study period. Of the 1881 patients, 1511 (80%) had at least one hospital readmission, of which 688 (37%) had at least one readmission for HF. 1407 (75%) patients had at least one non-HF related readmission.

The readmission rate for all-cause, HF related and non-HF related rehospitalisation for the overall cohort at 30-days was 20%, 10% and 12% respectively; and at 365-days was 66%, 40% and 58% respectively. The event rate (over 365 days) for all-cause, HF related and non-HF related rehospitalisation for the overall cohort was 3.4, 1.8 and 2.4 per person year respectively. Based on the limited mortality data, the overall mortality rate at 365 days was 15%. There were no significant between group differences in unadjusted mortality rate at 365 days (p=0.73).

Table 4.32: Number of hospital readmissions and unadjusted readmission rates for heart failure with preserved vs reduced ejection fraction

	HFpEF	HFrEF
No. of patients	971	910
All-cause readmissions		
Patients with ≥1 readmission	806	705
Patients with ≥2 readmissions	656	520
Patients with ≥3 readmissions	516	403
Total number of readmissions	3828	2769
HF related readmission		
Patients with ≥1 readmission	359	329
Patients with ≥2 readmissions	156	134
Patients with ≥3 readmissions	73	82
Total number of readmissions	676	604
Non-HF related readmission		
Patients with ≥1 readmission	763	644
Patients with ≥2 readmissions	443	448
Patients with ≥3 readmissions	319	321
Total number of readmissions	3152	2165
30-day readmission rate		
All-cause	20%	21%
HF related	9%	12%
Non-HF related	13%	12%
365-day readmission rate		
All-cause	68%	65%
HF related	40%	40%
Non-HF related	61%	56%
Event rate (365-days)		
All-cause/Person-year	3.4	3.5
HF admissions/Person-year	1.6	2.1
Non-HF admissions/Person-year	2.8	2.8

Abbreviations: HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

4.4.3. Comparison of statistical models for readmission outcomes

Table 4.33 presents the adjusted multivariate associations for rehospitalisation in HF with preserved and reduced ejection fraction according to the statistical model utilised; Logistic Regression, Cox-proportional Hazard and Negative Binomial models.

For HF related rehospitalisation, the 30-day readmission rate (according to logistic regression analysis) was significantly higher in the HFrEF ref group (OR= 1.64) compared to the HFpEF group, when adjusting for all covariates and clinical comorbidities. The adjusted 365-day readmission rate (according to logistic regression) was higher in the HFrEF group (OR= 1.17), however statistical significance was not achieved. The hazard ratio for time to first HF related readmission was significantly higher in the HFrEF group (HR=1.18), compared to the HFpEF group. Likewise, the adjusted event rate for HF related readmission was significantly higher in the HFrEF group (ERR=1.31) compared to the HFpEF group. When adjusting for confounders the rates of non-HF related rehospitalisation where similar between HFpEF and HFrEF groups, in all statistical models used. The adjusted all-cause rehospitalisation rates showed no statistical significance between the groups, however there was a trend toward increased 30-day all-cause readmission in HFrEF patients, driven by the increase rate of in HF readmissions in this group.

Apart from HFrEF, covariates independently associated HF related readmission in the long term (365-day odds, hazard for first readmission and recurrent event rate over 365 days) in this cohort included atrial fibrillation [(OR= 1.33; 95% CI 1.07-1.66), (HR= 1.27; 95% CI 1.11-1.46), (ERR= 1.30; 95% CI 1.08-1.55)], chronic kidney disease [OR= 1.71; 95% CI 1.31-2.22, (HR= 1.34; 95% CI 1.14-1.59), (ERR= 1.70; 95% CI 1.36-2.12)] and ischaemic heart disease (OR= 1.38; 95% CI 1.09-1.76). For ischaemic heart disease, a statistically significant increase in the adjusted risk of readmission was seen only for the 365-day OR, and not for the HR or ERR [(HR= 1.12; 95% CI 0.96-1.31), (ERR= 1.10; 95% CI 0.90-1.35)]. Estimates of OR, HR and ERR for other confounding variables for HF rehospitalisation can be found in Appendix 7.4.

Table 4.33: Multivariate associations for rehospitalisation in heart failure with preserved vs reduced ejection fraction using Logistic Regression, Cox-proportional Hazard and Negative Binomial models.

	Logistic Regression (Odds ratio)			Cox-proportional Hazard (Hazard ratio)		Negative Binomial (Event rate ratio)	
	HFpEF	HFrEF (30 days)	HFrEF (365 days)	HFpEF	HFrEF	HFpEF	HFrEF
All-cause admission Adjusted	Baseline	1.20 [0.94; 1.54]	1.08 [0.85; 1.36]	Baseline	1.03 [0.92; 1.15]	Baseline	1.04 [0.92; 1.18]
HF admission Adjusted	Baseline	1.64* [1.19; 2.26]	1.17 [0.94; 1.46]	Baseline	1.18* [1.03; 1.35]	Baseline	1.31* [1.10; 1.58]
Non-HF admission Adjusted	Baseline	0.95 [0.71; 1.28]	0.93 [0.74; 1.15]	Baseline	0.94 [0.83; 1.05]	Baseline	0.95 [0.83; 1.09]

Note: * denotes statistical significance. Hazard ratio's, odds ratios and event rate ratios expressed have 95% confidence intervals (CI). All models were adjusted for covariates of age, gender, marital status, and clinical co-morbidities.

Abbreviations: HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

4.5. Discussion

This study sought to compare the utility of different statistical models in the context of rehospitalisation, as a phenomenon in the natural history of HF. To the surprise of this author, between group differences were seen in HF-related readmission, in all three models over 12 months. Hence, from this data, no single model can definitively be judged as superior. This is the first study that the author is aware of to show a significant difference in rehospitalisation burden for HF related rehospitalisation between HFpEF and HFrEF, in that it was demonstrated that patients with HFrEF exhibit a higher burden of rehospitalisation over time.

The results of this study were somewhat unexpected, in that it was anticipated that the rates of rehospitalisation, according to first event analyses (i.e. logistic regression and Cox-proportional Hazards models), for HFrEF and HFpEF groups were going to be comparable. A finding which has been reported in other studies [198, 298]. The study hypothesis was that by including total rehospitalisation events into a statistical model that analyses recurrent events, a statistically significant burden of rehospitalisation would be demonstrated compared to the conventionally used first event statistical approaches, which failed to demonstrate a between group difference. And whilst the results of this study do not strictly match the hypothesis, they also do not support the null hypothesis; as the analysis of recurrent events did not yield a result of no difference in rehospitalisation burden in HFpEF and HFrEF groups.

The event rate for recurrent events over 365 days (by the negative binomial model), the hazard ratio time to first rehospitalisation (by Cox-proportional hazards) and the odds ratio for 365-day readmission rate (by logistic regression) are all measures of long-term rehospitalisation burden. Of these three models a statistically significant difference in HF related rehospitalisation was identified using their negative binomial and Cox-proportional hazard model, whereas the logistics regression did not demonstrate a between group statistical significance in 365-day readmission rate.

The greatest effect size for HF related rehospitalisation in the HFrEF was seen in the negative binomial model. Similar findings were seen in a post-hoc study of the CHARM-Preserved trial, which showed the greatest treatment effect of Candesartan was demonstrable with the analysis of recurrent events, specifically the Negative Binomial model when compared to the time-to-first event approach (cox proportional hazard model) [28]. The same finding was also seen in a post-hoc study of the EMPHASIS-HF trial, which showed greatest treatment effect of Eplerenone was achieved when analysing all

repeated admissions than by only studying the time to first readmission [186]. The authors of both studies stated described the inclusion of all events beyond the first event not only demonstrates a larger treatment effect, it also leads to a considerable gain in statistical power compared with a first event approach [27, 28].

In studying the effect of drugs and interventions on HF rehospitalisation burden, the treatment effect of the drug or intervention may increase or accumulate over time. Thus, the greatest effect of treatment may be seen in patients' second, third and fourth readmission etc. This notion has also been postulated by other authors [27, 28]. This particular argument does not hold up for an increasing effect size of HFrEF compared to HFpEF however. Worsening ejection fraction, which is associated with a natural progression of HFrEF [114], is also a predictor of increased risk of early first readmission [300, 301]. Thus, it could be argued that the progressive reduction in ejection fraction seen in HFrEF patients, may be the reason (or at least contributory), to the observed greater effect size in HFrEF when analysing total readmissions, in this study.

A recently published study from Spain [299] similarly investigated the role of analysing recurrent hospital admissions in HF patients. In this Spanish study, the authors aimed to characterise the burden of recurrent hospitalization following an admission for acute HF in patients with HFpEF vs HFrEF, using both first-event and recurrent event statistical approaches. A methodologically comparable study, the authors interestingly found no statistically significant between group differences in the analyses of first rehospitalisation for all admission types (i.e. all-cause, HF related, cardiovascular related and non-cardiovascular related). In the analysis of total admissions (recurrent event analysis), which was carried out using a negative binomial model, the authors identified a significant increase in the adjusted event rate for total non-cardiovascular related readmissions, there was no significant between group difference seen in other admission types, including HF related readmission.

The findings of increased first HF related readmission rates in the HFrEF group was unexpected and contrary to what has been previously been described (i.e. no difference). The underlying reasons for this are likely multifactorial, with the methodology for patients selected for study cohort plausibly being a key contributor. Only patients who had information on LVEF were included in this study cohort. It is possible that patients who had cardiac imaging performed represents those patients who were more unwell and had a greater priority for cardiac imaging in a resource limited setting. Thus, those excluded patients who did not have a cardiac imaging available may represent those patients who were more stable and is where imaging may have been performed by primary health providers or in

the private system. The exclusion of these HF patients, was just one of several limitations in this project.

This study has the expected limitations of observational research based on administrative data. Whilst the utilisation of administrative data sets in the study of HF populations is a validated and widely accepted method, there is no universally accepted and well-defined processes for the operationalisation of key study variables. As such, this study may have included/excluded admissions that other studies excluded/included. Moreover, the study cohort comprised of patients who did not reside in an aged care facility at the time of their index admission, so as to minimise the possible confounding of additional healthcare provision provided in these facilities. This inclusion/exclusion of such patients is typically not addressed in other studies. It is unclear, the effect of excluding these patients may have had on the study outcomes, particular as they may represent a more vulnerable subgroup of patients.

An assessment of ED visitation was not included in this study. It is unclear of the relationship between recurrent ED visitation and recurrent hospitalisation. Moreover, this study did not include sociodemographic characteristics such as socioeconomic status or cultural and linguistic diversity. Whilst both variables are undoubtedly important when considering HF rehospitalisation risk, due to methodological constraints these variables were compromised, especially given the primary focus of the study being on the methodical approach to the assessment of rehospitalisation, as oppose to a comprehensive assessment of the risk factors themselves.

Finally, a key limitation is the absence of complete mortality outcomes. It is unclear how some uncaptured deaths, which would not have been censored, may have impacted on the analyses. Albeit, there was no between group difference in 365-day mortality rate, where mortality data were available (i.e. if deaths occurred as an inpatient within the hospital network or if notified by other health services).

5. CHAPTER 5: Conclusion

This thesis describes and analyses the burden of rehospitalisation in HF populations. The first study presented sheds new light on the impact of cultural and linguistic diversity on HF patient outcomes. Utilising a new novel operation definition for CALD, this study demonstrated CALD patients have a graduated increased risk of rehospitalisation following an admission with acute HF. Increasingly, Australian health systems are required to serve a growing CALD population. A similar trend has been observed in many other developed countries. As attention is focussed upon the problem of repeat hospitalisation among patients with HF, CALD grouping may potentially be incorporated into models of readmission risk. Better awareness of the differential risk faced by CALD patients with HF, as well as improved understanding of the reasons that underpin this disparity, may result in targeted policies and interventions to curtail rehospitalisation in this vulnerable group.

The second study of this thesis focused on the different methodological approaches to assessing rehospitalisation burden in HF. This is the first study that the author is aware of that shows a significant difference between the burden from rehospitalisation for HFpEF and HFrEF. In the long term, the increase risk of HF rehospitalisation in HFrEF patients, is shown to a greater extent when analysing total recurrent events than is apparent from analysing first rehospitalisation only.

This thesis highlighted numerous methodological challenges in assessing rehospitalisation outcomes in HF patients, particular with respect to the utilisation of administrative datasets. In doing so, demonstrated the importance of well-defined operational processes and methodological approaches to i) identifying HF patients, ii) characterising the complexity of patients, and iii) the designation and evaluation of study outcomes (i.e. episodes of hospitalisation).

The research presented within this thesis hopes to inform future studies and health policy that examine rehospitalisation burden in HF populations, as well as health disparities of CALD groups in any disease context. This body of research has informed additional studies in other disease specific patient populations e.g. acute coronary syndromes and in gastrointestinal cancers (see appendix 7.5 and 7.6).

As the prevalence of HF is rising and patient populations becoming more diverse and complex, there is a resultant increasing strain on hospitals and wider healthcare systems. Only by first identifying and further understanding the differences in these evolving patient groups can the appropriate health

resource provision and health policy initiated, along with research into effective strategies, to mitigate any disparities identified.

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Appendices

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ORIGINAL ARTICLE

The impact of cultural and linguistic diversity on hospital readmission in patients hospitalized with acute heart failure

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Aims Health services worldwide face the challenge of providing care for increasingly culturally and linguistically diverse (CALD) populations. The aims of this study were to determine whether CALD patients hospitalized with acute heart failure (HF) are at increased risk of rehospitalization and emergency department (ED) visitation after discharge, compared to non-CALD patients, and within CALD patients to ascertain the impact of limited English proficiency (LEP) on outcomes.

Methods and results A cohort of 1613 patients discharged from hospital following an episode of acute HF was derived from hospital administrative datasets. CALD status was based on both country of birth and primary spoken language. Comorbidities, HF subtype, age, sex and socioeconomic status, and hospital readmission and ED visitation incidences, were compared between groups. A Cox proportional hazard model was employed to adjust for potential confounders. The majority of patients were classified as CALD [1030 (64%)]. Of these, 488 (30%) were designated as English proficient (CALD-EP) and 542 (34%) were designated CALD-LEP. Compared to non-CALD, CALD-LEP patients exhibited a greater cumulative incidence of HF-related readmission and ED visitation, as expressed by an adjusted hazard ratio (HR) [1.27 (1.02–1.57) and 1.40 (1.18–1.67), respectively]; this difference was not significant for all-cause readmission [adjusted HR 1.03 (0.88–1.20)]. CALD-EP showed a non-significant trend towards increased rehospitalization and ED visitation.

Conclusion This study suggests that CALD patients with HF, in particular those designated as CALD-LEP, have an increased risk of HF rehospitalization and ED visitation. Further research to elucidate the underlying reasons for this disparity are warranted.

Keywords Cultural and linguistic diversity • Limited English proficiency • Heart failure • Acute heart failure • Rehospitalization

Introduction

Heart failure (HF) is a complex clinical syndrome, associated with a significant burden of morbidity and mortality, including a high rate of rehospitalization. In order to optimize outcomes, contemporary studies have emphasized the need for better understanding of the clinical heterogeneity of the HF population.[1–4] Extending beyond the understanding of pathophysiological heterogeneity, the elucidation of sociodemographic factors may also reveal greater opportunities for targeted optimization. Although limited data are available with regard

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to the burden of HF in culturally diverse populations, recent opinion has highlighted the need for ongoing characterization and discussion of this subgroup amongst the HF community.[5,6]

In recent decades, accelerating global migration and urbanization have given rise to rapid cultural and linguistic diversification of populations worldwide.[7] The term 'culturally and linguistically diverse' (CALD) is a broad descriptor for individuals and communities, who possess ethnic/racial, cultural, religious and/or language characteristics that are different to those of the majority, in a given national context. In Australia, 26% of the population were born overseas—and of those born in Australia, 53% speak a language other than English at home.[8] In Australia, the United States (US), Canada, and the United Kingdom studies demonstrate that CALD groups suffer poorer health status compared to the general population.[9–12]

Studying the health impact of cultural and linguistic diversity has the inherent challenge of no universally accepted definition for CALD. As a construct, CALD is complex and abstract, characterized by the multiple dimensions of culture, ethnicity, religion, and language. Hence, the translation of the concept of CALD to its operationalization in research and policy has varied. Traditionally, studies have addressed the concepts of 'ethnicity' and 'language discordance' as methodologically separate entities. Data were collected on place of birth or self-identified ethnic group has been used to categorize ethnicity.[13] In addressing language discordance between healthcare providers and patients, as a variable for possible disparity, researchers frequently utilize data on patient's 'primary spoken language' or 'preferred spoken language' as collected by administrative staff during the hospital admission process. In studies taken place in nations where English is the predominantly spoken language, the term *limited English proficiency* (LEP) has been utilized by many researchers, where LEP denotes those patients who had a language other than English as their 'primary spoken language'.[14] Studies tend not to address concepts of ethnicity and language barriers simultaneously. In HF, e.g. North American studies have identified ethnicity as an important determinant of length of stay, mortality, and rehospitalization,[15–18] without addressing spoken language as a potential compounding factor.

The objective of this study was to assess the impact of cultural and linguistic diversity on clinical outcomes after hospitalization with acute HF, as primarily indexed by hospital readmission rates. In doing so, we present a novel operational definition of CALD, with the aim of better characterizing the continuum of diversity in the study cohort. We postulated that rates of rehospitalization would be greatest in CALD patients who were identified as having LEP.

Methods

Design and study population

A retrospective observational study was performed, utilizing a cohort of patients discharged with a principal diagnosis of HF from two acute metropolitan public hospitals, Footscray Hospital, and Sunshine Hospital, operating as a single health network in Melbourne, Western Health. The study period was from the 1 January 2013 to the 31 July 2016. Eligible patients were identified from hospital administrative datasets, using HF diagnostic codes based on the Australian Modified International Classification of Diseases, Tenth Revision (ICD10-AM). Patients hospitalized with a principle diagnosis of HF were identified by ICD10-AM codes (I50x, I11.0, I13.0, I13.2, I42x, I255, and J81).[19] To minimize the potential confounding effect of frequent additional care provided to specific subgroups, we excluded patients who were identified at the time of their discharge to be dialysis-dependent or who resided permanently in a nursing home.

Administrative data regarding patient rehospitalization, emergency department (ED) visitation and mortality were retrieved for the study period, extending to a minimum of 240 days from their index HF hospitalization. Only non-elective emergency hospitalizations and ED visitations were included: elective admissions, including dialysis, inpatient rehabilitation, and transfers to subacute care were excluded. Hospitalizations that involved transfers from another health service, or that resulted in transfers to another health service were also excluded. Consistent with previous methodological approaches with administrative datasets, non-elective admissions of less than 24 h duration (including time spent in the ED) were excluded.[20,21] Emergency department visitations were defined as those presentations, which resulted in direct discharge from emergency, not resulting in transfer to a ward environment. Complete mortality data were available if death occurred within the Western Health Network or if deaths occurred in the first 30 days after any hospitalization within the Western Health network. Beyond 30 days of a readmission, mortality data were incomplete and only available if notified by other health services.

Operational definitions

We defined CALD patients as those who were born outside of a principally English-speaking country and/or identified as speaking a language other than English as their primary spoken language, as recorded in hospital admission registration data. CALD patients were sub-classified as either CALD with English Proficiency (CALD-EP), based on English identified as being their primary spoken language—or as CALD with LEP (CALD-LEP), based on a documented primary spoken language being other than English. By definition, all non-CALD patients were considered to be English proficient (EP).

Covariate data and additional datasets

Data on covariates were obtained directly from the administrative database for sex, age at index HF admission, and marital status. ICD10-AM diagnostic codes were utilized to determine clinical comorbidities at the time of the index admission. The Charlson Comorbidity Index (CCI) was calculated as previously described.[22] A pre-existing diagnosis of HF was established for each individual in the cohort by identifying relevant ICD10-AM codes in hospital data, available from the three calendar years prior to the study period. Where available contemporaneous echocardiographic data were obtained from hospital records. Heart failure subtype was determined based on the reported left ventricular ejection fraction (EF): patients with an EF of <50% were classified as HF with reduced ejection fraction (HFrEF) and those with an EF of ≥50% were classified as HF with preserved ejection fraction (HFpEF).[23]

Socioeconomic status was determined by geospatial mapping, utilizing data from the Australian Bureau of Statistics, mapping residential addresses at the time of index admission to Statistical Area level 1 (SA1) codes.[24] SA1 codes denote small geographically defined residential areas that typically contain between 200 and 800 persons.[25] Individual SA1 codes are coregistered with Australian census data, including data relating to socioeconomic advantage and disadvantage. We utilized the 2011 census data, and the index of relative social advantage and disadvantage (IRSAD) as the preferred indication of socioeconomic status.[26]

Table 1 Study population baseline characteristics

	All patients (*n* = 1613)	Non-CALD (*n* = 583)	CALD-EP (*n* = 488)	CALD-LEP (*n* = 542)	*P*-value
Age (years), mean (SD)	77 (12)	75 (14)	76 (12)	80 (8)	<0.001
Age groups (years), *n* (%)					<0.001
0–64	224 (14)	126 (22)	72 (15)	26 (5)	
65–74	330 (20)	123 (21)	127 (26)	80 (15)	
75–84	611 (38)	178 (31)	171 (35)	262 (48)	
>84	448 (28)	156 (27)	118 (24)	174 (32)	
Gender, *n* (%)					0.001
Male	825 (51)	287 (49)	284 (58)	254 (47)	
Female	788 (49)	296 (51)	204 (42)	288 (53)	
Marital status, *n* (%)					<0.001
Single or widowed	654 (41)	250 (43)	172 (35)	232 (43)	
Married or *de facto*	835 (52)	264 (45)	280 (57)	291 (54)	
Separated or divorced	111 (7)	57 (10)	36 (7)	18 (3)	
Not stated	13 (1)	12 (2)	0 (0)	1 (0)	
SE status SA1, *n* (%)					0.003
1st quintile	662 (41)	213 (37)	218 (45)	231 (43)	
2nd quintile	446 (28)	164 (28)	125 (26)	157 (29)	
3rd quintile	268 (17)	114 (20)	80 (16)	74 (14)	
4th quintile	173 (11)	60 (10)	44 (9)	69 (13)	
5th quintile	61 (4)	31 (5)	19 (4)	11 (2)	
Country of birth, *n* (%)					<0.001
Australia	481 (30)	477 (82)	0	4 (1)	
Italy	189 (12)	—	73 (15)	116 (21)	
Malta	153 (9)	—	125 (26)	28 (5)	
Greece	100 (6)	—	19 (4)	81 (15)	
Macedonia	76 (5)	—	14 (3)	62 (11)	
Croatia	70 (4)	—	24 (5)	46 (8)	
England	48 (3)	48 (8)	0 (0)	0 (0)	
Vietnam	44 (3)	—	5 (1)	39 (7)	
Poland	43 (3)	—	26 (5)	17 (3)	
Other	409 (25)	58 (10)	202 (41)	149 (27)	
Primary spoken language, *n* (%)					<0.001
English	1071 (66)	583 (36)	488 (30)	0	
Italian	121 (8)	—	—	121 (22)	
Greek	94 (6)	—	—	94 (17)	
Macedonian	64 (4)	—	—	64 (12)	
Croatian	47 (3)	—	—	47 (9)	
Vietnamese	32 (2)	—	—	32 (6)	
Maltese	31 (2)	—	—	31 (6)	
Arabic	22 (1)	—	—	22 (4)	
Polish	16 (1)	—	—	16 (3)	
Other	115 (7)	—	—	115 (21)	
Heart failure type, *n* (%)					0.190
HFrEF	489 (30)	176 (30)	159 (33)	154 (28)	
HFpEF	534 (33)	169 (29)	170 (35)	195 (36)	
Unavailable	590 (37)	238 (41)	159 (33)	193 (36)	
Comorbidities, *n* (%)					
History of alcohol abuse	95 (6)	40 (6)	31 (6)	24 (4)	0.190
Atrial fibrillation	862 (53)	293 (50)	255 (52)	314 (58)	0.029
Chronic kidney disease	814 (50)	257 (44)	244 (50)	313 (58)	<0.001
Hypertension	1288 (80)	437 (75)	386 (79)	465 (86)	<0.001

Continued

Table 1 *Continued*

	All patients ($n = 1613$)	Non-CALD ($n = 583$)	CALD-EP ($n = 488$)	CALD-LEP ($n = 542$)	*P*-value
Prior history of heart failure	657 (41)	205 (35)	191 (39)	261 (48)	<0.001
Ischaemic heart disease	947 (59)	305 (52)	316 (65)	326 (60)	<0.001
Obesity	264 (16)	113 (19)	74 (15)	77 (14)	0.047
History of VTE	144 (9)	58 (10)	40 (8)	46 (8)	0.560
Sleep apnoea	186 (12)	66 (11)	61 (13)	59 (11)	0.707
Stroke	242 (15)	70 (12)	72 (15)	100 (18)	0.010
Diabetes	839 (52)	256 (44)	272 (56)	311 (57)	<0.001
Obstructive lung disease	737 (46)	261 (45)	229 (47)	247 (46)	0.631
History of malignancy	285 (18)	98 (17)	91 (19)	96 (18)	0.735
Dementia	173 (11)	46 (8)	39 (8)	88 (16)	<0.001
CCI (mean, SD)	5.5 (3.3)	5.0 (3.4)	5.6 (3.1)	6.0 (3.3)	<0.001

CALD-EP, culturally and linguistically diverse patients with English proficiency; CALD-LEP, culturally and linguistically diverse patients with limited English proficiency; CCI, Charlson comorbidity index; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; Non-CALD, non-culturally and linguistically diverse patients; SE, socioeconomic; SA1, statistical area 1 (see text); VTE, venous thromboembolism.

Table 2 Cumulative incidence rates and 95% confidence intervals for rehospitalization and emergency department visitation at specific times after discharge from the index admission

	All patients ($n = 1613$)	Non-CALD ($n = 583$)	CALD-EP ($n = 488$)	CALD-LEP ($n = 542$)
Emergency department visitation				
30 days	7.7% (5.4–9.9%)	6.2% (4.2–8.2%)	8.0% (5.6–10.4%)	8.7% (6.3–11.1%)
180 days	28.7% (24.7–32.5%)	23.3% (19.7–26.8%)	27.9% (23.7–31.8%)	34.8% (30.5–38.7%)
365 days	41.6% (37.1–45.8%)	33.8% (29.6–37.8%)	42.1% (37.4–46.5%)	48.9% (44.3–53.1%)
All-cause readmission				
30 days	17.3% (14–20.5%)	16.6% (13.5–19.5%)	16.3% (12.9–19.5%)	19.1% (15.7–22.4%)
180 days	41.9% (37.6–46%)	39.2% (35.1–43.1%)	40.1% (35.5–44.3%)	46.5% (42.1–50.6%)
365 days	55.6% (51.1–59.7%)	50.2% (45.8–54.2%)	54.8% (50–59.1%)	61.8% (57.4–65.7%)
HF-related readmission				
30 days	8.6% (6.2–11%)	7.3% (5.1–9.4%)	7.9% (5.4–10.2%)	10.8% (8.1–13.4%)
180 days	20.3% (16.8–23.7%)	17.1% (13.9–20.1%)	18.3% (14.7–21.7%)	25.7% (21.8–29.3%)
365 days	27.3% (23.3–31.1%)	21.6% (18.1–25%)	26.2% (22–30.1%)	34.2% (29.9–38.1%)

CALD-EP, culturally and linguistically diverse patients with English proficiency; CALD-LEP, culturally and linguistically diverse patients with limited English proficiency; HF, heart failure; Non-CALD, non-culturally and linguistically diverse patients.

The IRSAD was applied to each patient based on their SA1 code and expressed in quintiles relative to the Australian population.

Statistical analysis

Between-group differences in categorical variables were assessed with the χ^2 test. Survival methodology was used to investigate differences in time to first event between non-CALD, CALD-EP, and CALD-LEP groups. We performed separate analyses for time to first HF-related non-elective hospital readmission (HF rehospitalization), all-cause non-elective hospital readmission (all-cause rehospitalization), as well as time to first ED visitation. For all analyses, patients were censored at the end of follow-up or if recorded as deceased. Univariate analyses were performed using the non-parametric Kaplan–Meier and the log-rank test and ties in failure times were handled using Efron's method. To adjust for a potential confounding, Cox proportional hazard model was utilized, including the following covariates: age, sex, indicator variables for pre-existing HF, chronic kidney disease, hypertension, ischaemic heart disease, sleep apnoea, stroke, diabetes, obstructive lung disease, dementia, history of malignancy, marital status, and IRSAD score. All analyses were performed using the R software (R 3.4.2).[27]

Results

Baseline characteristics

In the 2013–2016 period, a total of 1613 patients were identified with an index non-elective admission in which HF was recorded as the principle diagnosis [mean age 79 ± 6 (SD) years; 51% male].

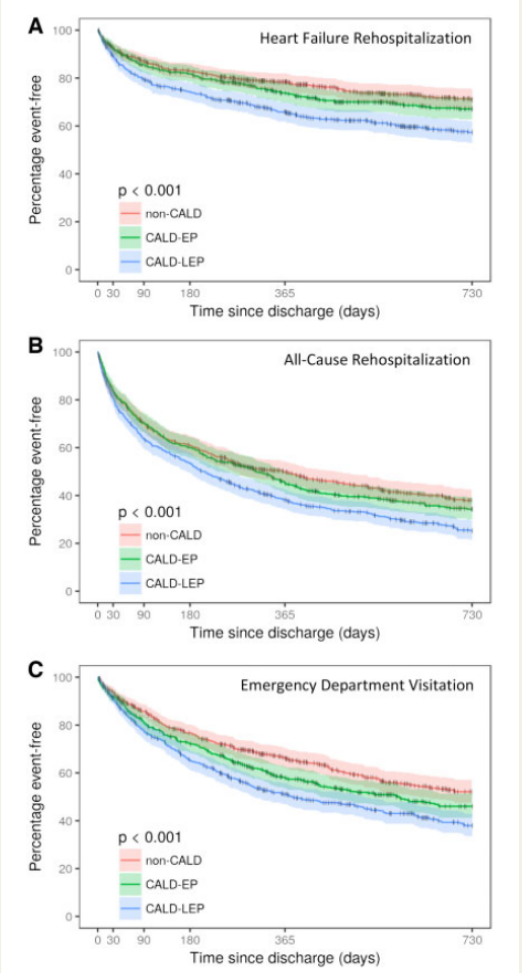

Figure 1 Fitted Kaplan–Meier curves for (*A*) heart failure rehospitalization, (*B*) all-cause rehospitalization, and (*C*) emergency department visitation. The observed pattern is consistent for emergency department visitation and rehospitalization and in both heart failure related and all-cause rehospitalization. CALD-LEP patients represent sooner than non-CALD patients and the rates CALD-EP rates are in-between. CALD-EP, culturally and linguistically diverse patients with English proficiency; CALD-LEP, culturally and linguistically diverse patients with limited English proficiency; Non-CALD, non-culturally and linguistically diverse patients.

The mean CCI was 5.5 and the two most prevalent comorbidities were hypertension (80%) and atrial fibrillation (53%). Echocardiogram data were available on 1005 patients (63%) and of these patients the prevalence of HFpEF was 52%.

There were 82 different counties of birth identified in the cohort. Of these, 10 were principally English-speaking countries. The most represented countries were Australia (30%), Italy (12%), Malta (9%), Greece (6%), Macedonia (5%), Croatia (4%), England (3%), Vietnam (3%), and Poland (3%). A total of 40 different primary spoken languages were identified in the cohort, the most common were English (66%), Italian (8%), Greek (6%), Macedonian (4%), Croatian (3%), and Vietnamese (2%) (see *Table 1*).

In terms of pre-specified CALD groupings, the HF cohort was divided approximately into thirds: 36% were classified as non-CALD, 30% were CALD-EP, and 34% were CALD-LEP, as shown in *Table 1*. CALD-LEP patients tended to be older at index admission and more likely to be female. The CALD-LEP group had higher proportions of pre-existing HF, atrial fibrillation, hypertension, chronic kidney disease, stroke, and dementia. In contrast, the CALD-EP group exhibited the highest proportion of ischaemic heart disease. The average length of in-hospital stay was 5 days and did not differ significantly between the three groups. In terms of socioeconomic status, 41% (662) of patients were in the lowest SA1 quintile, with a high proportion of CALD patients (CALD-EP and CALD-LEP) in the lowest SES quintile.

For those patients for whom HF subtype was known (63%), HF type was not associated with CALD grouping, or with rehospitalization or emergency visitation rates. As there was no association of HF type on a univariate analysis and availability of echocardiographic information was incomplete across the patient sample, this variable was not included in the multivariate analysis.

Readmission outcomes and survival analyses

Readmission rates at 30, 180, and 365 days are presented for each group in *Table 2*. At 30 days, the rate of all-cause rehospitalization for the overall cohort was 17.2%. The observed pattern on the fitted Kaplan–Meier curves was consistent for HF-related readmission, all-cause readmission, and ED visitation (see *Figure 1*). CALD-LEP patients tended to have rehospitalization sooner than non-CALD patients, whereas CALD-EP rehospitalization rates tended to be intermediate and fall between the CALD-LEP and non-CALD groups. Given that this finding was broadly consistent with the relative distribution of increased age and comorbidities among the three groups, a Cox proportional hazards model was subsequently fit to adjust for potential confounding. Adjusted and unadjusted hazard ratios are displayed in *Table 3*. While adjustment decreases the size of the effect, evidence of an independent effect of CALD grouping remained for HF-related readmission. Estimates of the hazard ratios for confounding variables for HF rehospitalization are displayed in *Table 4*.

Apart from CALD-LEP, covariates independently associated with HF-related readmission in this cohort included atrial fibrillation, chronic kidney disease, obstructive lung disease, pre-existing HF diagnosis, ischaemic heart disease, and sleep apnoea. Conversely, the presence of diabetes and a history of malignancy appeared to predict reduced HF-related readmission.

Overall mortality rate at 30 days and 365 days, where 1.7% and 17%, respectively. There were no significant between group differences in unadjusted mortality rate at 30 days ($P = 0.5$) and 365 days ($P = 0.12$).

Discussion

In the context of a multicultural metropolitan health service, this study demonstrates a graduated risk of HF rehospitalization

Table 3 Univariate and multivariate associations for rehospitalization and emergency department visitation, using three different CALD classification models

	Non-CALD	CALD-EP	CALD-LEP	Non-CALD	CALD (CALD-EP + CALD-LEP)	EP (non-CALD + CALD-EP)	CALD-LEP
Emergency department visitation							
Unadjusted	Ref	1.23[a] (1.03–1.47)	1.52[a] (1.29–1.79)	Ref	1.38[a] (1.19–1.60)	Ref	1.37[a] (1.20–1.58)
Adjusted	—	1.15 (0.96–1.38)	1.40[a] (1.18–1.67)	—	1.28[a] (1.09–1.49)	—	1.30[a] (1.13–1.51)
All-cause readmission							
Unadjusted	Ref	1.10 (0.94–1.28)	1.38[a] (1.19–1.59)	Ref	1.24[a] (1.09–1.41)	Ref	1.32[a] (1.16–1.49)
Adjusted	—	0.93 (0.79–1.09)	1.03 (0.88–1.20)	—	0.98 (0.86–1.12)	—	1.07 (0.94–1.22)
HF-related readmission							
Unadjusted	Ref	1.21 (0.97–1.51)	1.64[a] (1.34–2.02)	Ref	1.43[a] (1.19–1.73)	Ref	1.50[a] (1.26–1.78)
Adjusted	—	1.04 (0.83–1.30)	1.27[a] (1.02–1.57)	—	1.15 (0.95–1.40)	—	1.24[a] (1.04–1.49)

Hazard ratio's (HR) and 95% confidence intervals (CIs) are estimated by Cox proportional hazard model, with and without adjustment for covariates of age, gender, marital status, SA1 quintile, atrial fibrillation, chronic kidney disease, hypertension, history of heart failure, ischaemic heart disease, sleep apnoea, stroke, diabetes, obstructive lung disease, history of malignancy, dementia, and Charlson comorbidity index.
CALD-EP, culturally and linguistically diverse patients with English proficiency; CALD-LEP, culturally and linguistically diverse patients with limited English proficiency; ED, emergency department; EP, English proficient patients (includes non-CALD and CALD-EP); HF, heart failure; Non-CALD, non-culturally and linguistically diverse patients.
[a]Statistical significance.

associated with CALD grouping. An increased incidence of HF-related readmission and ED visitation was observed in CALD-LEP patients when compared with non-CALD patients. This association persisted after multivariable adjustment for comorbidities and socioeconomic status. The CALD-EP group appeared to carry an intermediate risk, exhibiting (non-statistically significant) trends towards earlier rehospitalization and ED visitation, when compared with their non-CALD counterparts.

This study adds to the body of evidence that has shown language discordance[28] and ethnicity are proxies for adverse health outcomes in HF and other medical populations.[29–31] Few studies, have sought to address ethnic diversity and language discordance concurrently, specifically in a HF population. CALD status, based primarily on country of birth (nativity) is operationally equivalent to the designation of ethnic minorities used in other studies.[32–37] Likewise, the CALD subgroup (i.e. CALD-LEP) based on identifier of primary spoken language is operationally comparable to studies investigating minority groups with language discordance[28,31,38–40] and for low acculturation.[41] Our use of a novel framework for the operational definitions for CALD and CALD subgroups (CALD-EP and CALD-LEP) was intended to better represent the continuum of diversity and disparity in the CALD population and to help ascertain if patient outcomes change along this continuum. The CALD-LEP subgroup likely represents one end of the continuum of diversity, at which there exists a greater potential for lack of acculturation, in addition to a potential language barrier, both of which have health disparity implications. In contrast, CALD-EP likely denotes less risk of a barrier to communication, but with a variable component of acculturation. The fact that these designations appeared to capture the extent of clinical risk, in this case indexed by HF rehospitalization, while not validating this framework entirely, lends support to it.

Nativity and language discordance are but two identifiers for a complex heterogeneous group of patients. The nature and direction of the relationship between these identifiers and the concept of cultural and linguistic diversity cannot be assumed to be orthogonal. To this effect, the assumption does not hold that the health disparity in the CALD population will change commensurately to variations of the identifying variables. For example; if a cohort of CALD-LEP patients became proficient in English, this would not confer a commensurate improvement in their health status. English proficiency is likely associated also with other variables, latent or otherwise, that were not included in this study; variables that may be difficult to record or even define, such as health literacy and acculturation. While interventions focused on improving communication between patient and health care provider may capture causal effects (e.g. improved medication adherence through better communication), they may not concomitantly address the pathways from other potential influences—such as acculturation, socioeconomic status, health literacy, stigma, and cultural beliefs. This in mind, health strategies aimed to address health disparity in CALD populations undoubtedly will require a multipronged approach, rather than one focused exclusively on language.

Capturing the multidimensional nature of CALD populations by using any one or several measures is inherently challenging. In many research settings, there are limited variables which can be practicably utilized to represent the spectrum and heterogeneity of CALD patients. In the case of administrative health data sets, the collected information is largely pragmatic and categorical, without a focus on qualitative measures. Future studies, may incorporate the use of multiple categorical and continuous measures (e.g. time since migration and level of English proficiency), which look to better characterize the dimensionality and continuum of diversity in CALD populations. Such research could augment the interpretations drawn on the basis of studies that have utilized any single or multiple categorical indicators.

In understanding the findings of this study, numerous potential mechanisms for these differences can be discussed. Poor communication between patients, their families, and health care providers may

Table 4 Predictors for heart failure rehospitalization in the multivariate survival analysis

Variables	Hazard ratio	95% confidence interval	*P*-value
CALD group			
Non-CALD	Ref		
CALD-EP	1.04	0.82–1.30	0.76
CALD-LEP	1.27	1.02–1.57	0.03
Age groups			
0–64	Ref		
65–74	1.04	0.74–1.47	0.81
75–84	1.11	0.80–1.54	0.53
85+ over	1.22	0.86–1.74	0.27
Gender			
Female	1.12	0.93–1.34	0.24
Male	Ref		
Marital status			
Single or widowed, separated or divorced	Ref		
Married or *de facto*	1.01	0.84–1.22	0.90
Socioeconomic status (SA1 quintiles)			
1st quintile	Ref		
2nd quintile	0.97	0.78–1.20	0.79
3rd quintile	1.13	0.89–1.44	0.31
4th quintile	1.18	0.89–1.57	0.26
5th quintile	0.75	0.41–1.34	0.33
Comorbidities			
History of alcohol abuse	0.77	0.49–1.19	0.24
Obstructive lung disease	1.27	1.06–1.52	0.01
Atrial fibrillation	1.57	1.31–1.89	<0.001
Chronic kidney disease	1.89	1.48–2.42	<0.001
Hypertension	1.16	0.85–1.57	0.35
History of heart failure	1.23	1.03–1.46	0.02
Ischaemic heart disease	1.37	1.12–1.69	<0.01
History of VTE	1.1	0.83–1.46	0.52
Sleep apnoea	1.62	1.27–2.06	<0.001
Stroke	0.96	0.75–1.23	0.76
Diabetes	0.72	0.56–0.93	0.01[a]
History of malignancy	0.69	0.53–0.89	0.01[a]
Dementia	0.82	0.63–1.08	0.16
Charlson comorbidity index			
0–2	Ref		
3–4	1.34	0.91–1.97	0.14
5–6	1.73	1.12–2.68	<0.01
7–8	2.19	1.32–3.65	<0.01
9+	2.35	1.33–4.17	<0.01

[a]Factors were associated with statistically significant reduced readmission, rather than increased readmission.

result in suboptimal medical treatment, or even where medical treatment is optimal, poor understanding may result in inappropriate presentation to a health care organization. HF is associated with intermittent decompensation and serial readmission, in which outcomes are enhanced by interdisciplinary systems of care[42] and patient education,[43] and negatively associated with lower socioeconomic status.[44] Whilst socioeconomic status was indexed, reduced variation in the cohort may have resulted in limited statistical power, given that the majority were in the lowest two quintiles. Disparities in educational level and health literacy, in addition to variation in health care beliefs and behaviours, may interact with CALD status and were not completely controlled for in our patient sample. The CALD group in this study cohort were represented by 75 different countries of origin and 40 different languages. This very heterogeneous group, is in contrast to the homogeneity of non-CALD patients, which comprise of individuals predominantly of whom are of Anglo-Celtic ancestry.[45] Thus, we are unable to exclude biological differences that may have contributed to the between group differences observed.

The clinical characteristics of the cohort in this study is similar to that of contemporary HF studies in terms of multimorbidity and proportion of HFpEF and HFrEF.[46,47] In this study, clinical comorbidities associated with early rehospitalization included chronic kidney disease, atrial fibrillation, ischaemic heart disease, sleep apnoea, obstructive lung disease, and hypertension, which are in keeping with previous studies.[48,49] The proportion of HF subtypes were equally represented and neither were associated with differential risk of rehospitalization.

Two specific observations in this study require comment. A negative association was found between diabetes and readmission, which is in contrast to other studies.[50] Since the presence of diabetes contributes to ischaemic heart disease and chronic kidney disease, both of which were positive predictors in the multivariate model, we postulate that the adjusted group represents relatively uncomplicated or well-controlled diabetics. Malignancy was also negatively associated with readmission. This finding may be misleading, as planned or elective admissions, which include chemotherapy treatments, were excluded from analyses.

Our study has the expected limitations of observational research based on administrative data. This study was confined to broad definitions of the culture and language groups studied, which are unlikely to fully capture the capacities of individual patients in regards to communication, self-care and accessing of health care services—for which prospective qualitative studies would be necessary. Whereas it is intuitive that poorer outcomes will be observed in CALD groups, the extent to which it may interact with health literacy and other social determinants of health needs to be elucidated. A key limitation is the absence of complete long-term mortality outcomes, whilst complete mortality data were available for the first 30 days, death status was only available beyond 30 days if the individual died as an inpatient in the hospital network or if notified by other health services. As a result, some uncaptured deaths that occurred beyond 30 days out of hospital were not censored in the survival analysis.

Of note, the use of interpreter services in the care of CALD patients in this cohort was not determined. Further, we cannot exclude that an excess of ED visitations in CALD patients in part

reflects health care beliefs and/or barriers to access, favouring use of a hospital ED over consultation with a local medical officer/general practitioner. Finally, our study cohort did not include indigenous patients in significant numbers and cannot address the effect of indigenous status on outcomes in this disease context.

Conclusion

This study sheds new light on the impact of cultural and linguistic diversity on HF patient outcomes, demonstrating CALD patients are at greater risk of rehospitalization following an admission with acute HF. Similar to other developed countries, Australian Hospital systems serve an increasingly growing CALD population. As attention is focused upon the problem of repeat hospitalization among patients with HF, CALD grouping may potentially be incorporated into models of readmission risk. Better awareness of the differential risk faced by CALD patients with HF, as well as improved understanding of the reasons that underpin this disparity, may result in targeted policies and interventions to curtail rehospitalization in this vulnerable group.

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Appendix 7.2

Examples of PowerPivot formulas used for key outcome measure abstraction

- **Identifying English proficient and Limited English proficient subjects:**
  =IF([Language Spoken]="English",1,0)

- **Identifying a subjects first heart failure admission in study period:**
  =if([Separation Date] >= DATE(2013,1,1) && [Separation Date] <= DATE(2015,12,31) && CALCULATE(MIN([SeparationDate]), ALLEXCEPT(Admissions,Admissions[ID Number]),Admissions[HF Admission Flag] = 1)=[Separation Date],1,0)

- **Days since discharge until admission:**
  =CALCULATE(MIN(Admissions[Days since initial HF separation]), ALLEXCEPT(Admissions,patients[ID Number]),Admissions[Days since initial HF separation]>0)

- **Heart failure related readmissions at 180 days:**
  =if([Days since initial HF separation] >0 && [Days since initial HF separation]<=180,1,0)

- **Charlson Co-morbidity Index**
  =[C-Rheum]+[C-Mets]+[C-CLD_Mod-Severe]+[C-Malig]+[C-HIV-AIDS]+[C-DM_Compl]+[C DM_Uncompl]+[C-Renal]+[C-Plegia]+[C-CLD_Mild]+[C-PepticUlcer]+[C-CPD]+[C-CVD]+[C-Dementia]+[C-PVD]+[C-CCF]+[C-AMI]

- **Closest Echocardiogram result to patients Index admission**
  =if(NOT(ISBLANK(COUNTROWS(RELATEDTABLE(Admissions)))),1. * ABS(ROUND((Echo[Study Date] CALCULATE(MIN(Admissions[admissionDate]),Admissions[IDNumber],Admissions[First HF Admission in period]=1)),2)),BLANK())

Appendix 7.3

ICD10-AM Diagnosis Codes used for each condition

Acute Kidney Failure
Codes: N170, N171, N172, N179

Alcohol
Codes: F10*

Asthma
Codes: J450, J451, J458, J459, U833

Atrial Fibrillation
Codes: I48*

CKD (Chronic Kidney Disease)
Codes: N181, N182, N183, N184, N185, U871

Chronic Liver disease (Mild) (Charlson Score: 1)
Codes: B18*, K700, K701, K703, K709, K713, K714, K715, K717, K73*, K74*, K760, K762, K763, K764, K768, K769, Z944

Chronic Liver disease (Mod-Severe) (Charlson Score: 3)
Codes: I850, I859, I864, I982, K704, K711, K721, K729, K765, K766, K767

Chronic obstructive airway disease
Codes: J440, J441, J448, J449, U832

Cerebrovascular disease (Charlson Score: 1)
Codes: H340, I60*, I61*, I62*, I63*, I64*, I65*, I66*, I67*, I68*, I69*, G45*, G46*

Delirium
Codes: F050, F051, F058, F059

Dementia (Charlson Score: 1)
Codes: F00*, F01*, F02*, F03*, F051, G311

Diabetes Mellitus (Complicated) (Charlson Score: 2)
Codes: E102*, E103*, E104*, E105*, E107*, E112*, E115*, E117*, E122*, E123*, E124*, E125*, E127*, E132*, E133*, E134*, E135*, E137*, E142*, E143*, E144*, E145*, E147*

Diabetes Mellitus (Uncomplicated) (Charlson Score: 1)
Codes: E100*, E101*, E106*, E108*, E109*, E110*, E111*, E116*, E118*, E119*, E120*, E121*, El26*, E128*, El29*, E130*, E131*, E136*, E138*, E139*, E140*, E141*, E146*, E148*, E149*

HIV (Charlson Score: 6)
Codes: B20*, B21*, B22*, B24*

Hypertension
Codes: I10, U823

Ischaemic Heart Disease inc. Acute Subendocardial MI
Codes: I20*, I21*, I22*, I23*, I24*, I25*, U821

Myocardial infarction (Charlson Score: 1)
Codes: I21*, I22*, I252

Malignancy (Charlson Score: 2)
Codes: C*, Z08*, Z85*

Metastases (Charlson Score: 6)
Codes: C77*, C78*, C79*, C80*

Obesity
Codes: E660, E661, E662, E668, E669, U781

Peptic Ulcer (Charlson Score: 1)
Codes: K25*, K26*, K27*, K28*

Plegia (Charlson Score: 2)
Codes: G041, G114, G801, G802, G81*, G82*, G830, G831, G832, G833, G834, G839

Peripheral vascular disease (Charlson Score: 1)
Codes: I70*, I71*, I731, I738, I739, I771, I790, I792, K551, K558, K559, Z958, Z959

Renal (Charlson Score: 2)
Codes: I120, I131, N032, N033, N034, N035, N036, N037, N052, N053, N054, N056, N057, N18*, N19*, N250, Z490, Z491, Z492, Z940, Z992

Rheumatoid (Charlson Score: 1)
Codes: M05*, M06*, M315, M32*, M33*, M351, M353, M360

Sleep Apnoea
Codes: G4730, G4731, G4732, G4733, G4739

Type 2 Diabetes Mellitus
Codes: E11*

Venous thromboembolism
Codes: I260, I269, I801, I802, I803, I808, I809, I828, I829

Appendix 7.4

Covariant association with Heart failure related rehospitalisation in the multivariate analysis using Logistic Regression, Cox-proportional Hazard and Negative Binomial models.

Covariant	OR (30d)	OR (365 days)	HR (Cox)	Event Rate
HFrEF	1.64 [1.19; 2.26]	1.17 [0.94; 1.46]	1.18 [1.03; 1.35]	1.31 [1.10; 1.58]
Gender (Male)	1.19 [0.85; 1.67]	0.91 [0.72; 1.14]	0.95 [0.82; 1.09]	0.96 [0.80; 1.16]
Age				
<65 yrs	0.02 [0.00; 3.58]	0.12 [0.00; 6.07]	0.24 [0.01; 4.36]	0.12 [0.00; 4.27]
65 – 70 yrs	0.26 [0.01; 4.78]	0.30 [0.03; 2.99]	0.49 [0.08; 2.96]	0.54 [0.06; 4.47]
70 – 75 yrs	0.20 [0.01; 5.68]	0.62 [0.04; 8.70]	0.87 [0.12; 6.57]	0.90 [0.08; 10.05]
80- 85 yrs	0.41 [0.02; 9.31]	0.71 [0.06; 8.59]	0.78 [0.12; 5.30]	1.31 [0.14; 12.70]
85+ yrs	3.23 [0.09; 121.73]	5.04 [0.20; 126.20]	4.61 [0.50; 42.23]	4.86 [0.33; 70.73]
HF history	1.19 [0.86; 1.64]	1.13 [0.91; 1.41]	1.19 [1.04; 1.36]	1.18 [0.99; 1.42]
AF	1.00 [0.73; 1.38]	1.33 [1.07; 1.66]	1.27 [1.11; 1.46]	1.30 [1.08; 1.55]
COPD	0.85 [0.62; 1.18]	1.06 [0.85; 1.32]	1.05 [0.92; 1.21]	1.10 [0.92; 1.32]
Chr Kidney Disease	1.77 [1.17; 2.69]	1.71 [1.31; 2.22]	1.34 [1.14; 1.59]	1.70 [1.36; 2.12]
DM	0.57 [0.38; 0.86]	0.57 [0.43; 0.75]	0.60 [0.50; 0.71]	0.56 [0.45; 0.71]
sleep apnoea	1.19 [0.70; 2.01]	1.17 [0.83; 1.67]	1.22 [0.99; 1.51]	1.11 [0.83; 1.49]
obesity	1.07 [0.67; 1.69]	1.19 [0.88; 1.62]	1.18 [0.98; 1.42]	0.96 [0.74; 1.23]
ccmi 3-4	0.71 [0.38; 1.31]	1.25 [0.85; 1.84]	1.41 [1.07; 1.84]	1.29 [0.92; 1.81]
ccmi 5-6	1.34 [0.71; 2.50]	1.87 [1.23; 2.86]	2.04 [1.53; 2.71]	2.32 [1.62; 3.33]
ccmi 7-8	1.78 [0.86; 3.70]	2.59 [1.56; 4.28]	3.08 [2.22; 4.27]	2.87 [1.88; 4.37]
ccmi 9+	1.95 [0.92; 4.13]	3.03 [1.80; 5.10]	3.36 [2.40; 4.71]	3.96 [2.57; 6.11]
stroke	0.90 [0.59; 1.38]	0.98 [0.73; 1.31]	0.86 [0.72; 1.03]	0.96 [0.76; 1.22]
dementia	1.30 [0.82; 2.05]	1.06 [0.75; 1.49]	0.99 [0.81; 1.21]	0.97 [0.74; 1.28]
hypertension	1.06 [0.64; 1.73]	0.86 [0.61; 1.20]	1.14 [0.91; 1.43]	0.81 [0.61; 1.07]
IHD	0.96 [0.67; 1.38]	1.38 [1.09; 1.76]	1.12 [0.96; 1.31]	1.10 [0.90; 1.35]
single	0.88 [0.64; 1.22]	1.04 [0.83; 1.30]	1.00 [0.87; 1.15]	0.99 [0.82; 1.18]

Appendix 7.5

CONFIDENTIAL

Gastrointestinal cancer treatment and survival in culturally and linguistically diverse patients: Exploring health disparities in an Australian population.

Protocol No: 0001
Version: Version 1.0
Date: 26-11-2019

Principal Investigator: **A/Prof Justin Yeung**
Associate Investigator: **Dr Michael Seman**
Associate Investigator: **Mr Cuong Duong**
Associate Investigator: **Mr Marcos Perini**
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Associate Investigator: **Prof Peter Gibbs**
Associate Investigator: **Dr Belinda Lee**
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Associate Investigator: **Mr Michael Hii**

Western Health

Appendix 7.6

INTERNAL MEDICINE JOURNAL

RACP Specialists. Together

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BRIEF COMMUNICATIONS

Impact of limited English proficiency on presentation and outcomes of patients undergoing primary percutaneous coronary intervention for ST-elevation myocardial infarction

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Key words
acute myocardial infarction, English proficiency, percutaneous coronary intervention.

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Abstract

Doctor–patient language discordance has been shown to lead to worse clinical outcomes. In this study of patients undergoing primary percutaneous coronary intervention for ST-elevation myocardial infarction at an Australian health service, we demonstrated that limited English proficiency (LEP) is an independent predictor of prolonged symptom-to-door time, but does not lead to worse 30-day mortality compared with English-proficient patients. More effort needs to be placed in providing public health education in varied languages to encourage early presentation to hospital for patients with LEP.

Increasing global migration leading to cultural and linguistic diversity in society has presented challenges in healthcare delivery, as a growing problem of language discordance between healthcare providers and patients arises. In Australia, recent census data have shown that over one-quarter of Australia's population was born overseas and nearly one-fifth of the population speak a language other than English at home.[1] Language barriers can compromise patient–provider communication and negatively affect the ability to deliver safe and effective healthcare.[2,3]. Previous studies have shown that in predominantly English-speaking countries, limited English proficiency (LEP) is associated with prolonged hospital length of stay, higher readmission rates and poorer self-reported health status.[4–8] Within cardiology practice, patients with LEP have been shown to have lower rates of cardiac catheterisation and percutaneous coronary intervention (PCI) following presentation with an acute coronary syndrome (ACS).[9] However, the impact of LEP on delays to cardiac catheterisation and outcomes in patients with ST-elevation myocardial infarction (STEMI) treated with PCI has not been specifically investigated. In this study, we aimed to examine whether among patients with STEMI undergoing primary PCI, LEP was associated with longer delays to reperfusion and worse clinical outcomes.

This study was performed at a multi-centre tertiary health service in Melbourne, Australia. The health service treats one of the most culturally diverse communities in the state of Victoria, with 38% of the population speaking a language other than English at home.[1] Routinely collected data on all patients undergoing PCI includes baseline demographics, procedural information, in-hospital complications and 30-day follow-up events as part of the Victorian Cardiac Outcomes Registry (VCOR) – a multi-centre state-wide PCI registry, including all public and private hospitals in Victoria, Australia which has been described previously.[10,11] All patients are provided with

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Conflict of interest: None.

information on the VCOR data collection process and there is an opt-out consent process, with no patients at this health service having declined involvement to date. In this study, all STEMI patients undergoing primary PCI at this health service between 15 July 2013 and 31 December 2016 were included and data collected as part of VCOR were analysed. Patients who had PCI post-thrombolysis or had an in-hospital STEMI were excluded.

In this study, the health service's patient administration system database was used to identify the patient's primary spoken language and country of birth. These data are documented at the time of hospital admission by a clerk and checked at each subsequent hospital attendance. Patients who identified a language other than English as their primary spoken language were defined has having LEP. All patients who identified English as their primary spoken language were defined as English proficient (EP).

Data for continuous variables were expressed as means and standard deviations whilst categorical variables were expressed as numbers of people and percentages. Categorical variables were compared using the Chi-squared test or the Fisher exact test. Continuous variables were compared using the *t*-test or Mann Whitney *U*-test. Logistic multi-variable regression analysis was used to identify independent predictors of prolonged symptom-to-door time using variables with a *P*-value of less than 0.1 on univariate analysis. A two-sided *P*-value of less than 0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS statistics software version 24 (IBM, Armonk, NY, USA).

The study was reviewed and granted ethical approval by the ethics committee at Western Health.

During the study period, 650 patients underwent primary PCI for STEMI and were included in this study. Of this, 98 patients (15.1%) were classified as LEP based on their self-reported primary spoken language. Among the LEP patients, the most commonly spoken languages were Vietnamese (23.4%, $n = 23$) and Greek (8.2%, $n = 8$). Of the EP patients, 195 (35.3%) were born outside of Australia, New Zealand, the United Kingdom or North America.

The LEP group was slightly older (mean age 65.6 years vs 58.8 years, $P < 0.01$) with a greater proportion of females (31.6% vs 19.2%, $P < 0.01$). There were no other significant differences in baseline demographics and comorbidities, including in the history of previous PCI or coronary artery bypass graft surgery (Table 1). Presentation with out-of-hospital cardiac arrest or cardiogenic shock was similar in the two groups. Pre-hospital notification by paramedics was also similar. There were no significant procedural differences in terms of PCI success, use of drug-eluting stents or lesion complexity between the groups.

Door-to-balloon times were similar in both the LEP and EP groups (71 min (interquartile (IQR) 48–112) vs

Table 1 Comparison of baseline and procedural characteristics and outcomes in English proficient and limited English-proficient patients

	English proficient (EP)	Limited English proficiency (LEP)	*P*-value
Number	552	98	
Mean age ± SD (years)	58.8 ± 12.7	65.6 ± 11.9	<0.01
Male, *n* (%)	446 (80.8)	67 (68.4)	<0.01
Mean body mass index (kg/m^2)	28.8 ± 5.8	26.3 ± 4.7	<0.01
Diabetes, *n* (%)	94 (17.0)	23 (23.5)	0.13
Stage 4–5 chronic kidney disease (estimated glomerular filtration rate < 30 mL/min/1.73 m^2), *n* (%)	12 (2.2)	4 (4.1)	0.26
Previous percutaneous coronary intervention, *n* (%)	63 (11.4)	7 (7.1)	0.21
Previous coronary artery bypass graft surgery, *n* (%)	9 (1.6)	1 (1.0)	0.65
Out-of-hospital cardiac arrest, *n* (%)	35 (6.3)	8 (8.2)	0.50
Cardiogenic shock on presentation, *n* (%)	59 (10.7)	13 (13.3)	0.45
Pre-hospital notification, *n* (%)	293 (53.1)	45 (45.9)	0.19
Radial access, *n* (%)	271 (49.1)	44 (44.9)	0.44
AHA/ACC type B2/C lesion, *n* (%)	303 (54.9)	63 (64.3)	0.08
Drug-eluting stent used, *n* (%)	359 (65.0)	73 (74.5)	0.68
Successful percutaneous coronary intervention, *n* (%)	527 (95.5)	92 (93.9)	0.50
Length of stay in days, median (IQR)	3 (3–3)	3 (3–4)	0.50
In-hospital mortality, *n* (%)	29 (5.3)	7 (7.1)	0.45
In-hospital major adverse cardiac events, *n* (%)	32 (5.8)	7 (7.1)	0.61
In-hospital bleeding (BARC type 2 or more), *n* (%)	16 (2.9)	2 (2.0)	0.09
30-Day mortality, *n* (%)	37 (7.8)	8 (9.1)	0.69
30-Day unplanned readmissions, *n* (%)	46 (9.7)	8 (9.1)	0.85

ACC, American College of Cardiology; AHA, American Heart Association.

68 min (IQR 44–103), $P = 0.21$). Total ischaemic time defined as time from symptom onset to first balloon inflation in a coronary artery was significantly longer in the LEP group (281 min (IQR 160–720) vs 203 min (IQR 150–350), $P < 0.01$), driven by longer symptom-to-door times (193 min (IQR 94–502) vs 120 min (IQR 85–226), $P < 0.01$) (Fig. 1). Median symptom-to-door time (STDT) for the entire cohort was 124 min. Patients with a STDT greater than 124 min were considered to have a prolonged STDT. On multiple logistic regression analysis, LEP was an independent risk factor for prolonged STDT (odds ratio (OR) 1.63, 95% confidence interval (CI) 1.05–2.54; $P = 0.03$) whilst a history of PCI or coronary artery bypass graft surgery (OR 0.50, 95% CI 0.30–0.83; $P < 0.01$) and pre-hospital notification (OR 0.64, 95% CI 0.47–0.87; $P < 0.01$) were found to be independent protective factors for prolonged STDT.

The median length of hospital stay was equal between the two groups at 3 days ($P = 0.70$). There was no difference in in-hospital mortality and major adverse cardiac events (MACE) between the two groups (7.1% vs 5.3%, $P = 0.45$ and 7.1% vs 5.8%, $P = 0.61$ respectively). A total of 85.5% in the EP group and 89.8% in the LEP group had 30-day follow up completed ($P = 0.26$). There was no significant difference in 30-day mortality ($P = 0.69$) or unplanned readmissions ($P = 0.85$) between the two groups.

Discussion

In our study, we found a marked difference in symptom-to-door time between LEP and EP patients, with median symptom-to-door time being 73 min longer in LEP patients. LEP was also found to be an independent predictor of prolonged symptom-to-door time. However, once patients entered the hospital system, there were no apparent differences in treatment times or outcomes. In-hospital and 30-day mortality were both slightly higher in the LEP group, but these differences were not statistically significant, possibly due to a small sample size.

Recent focus in STEMI care has been on reducing delays to reperfusion by both encouraging patients to present early and improving systems of care of STEMI management. In Australia, the National Heart Foundation health promotion organisation has for many years run a media campaign to educate the public on potential symptoms of an acute myocardial infarction (AMI).[12] Yet the significantly longer symptom-to-door time in LEP patients however suggests that knowledge on AMI symptoms may be deficient in the LEP population. This has also been demonstrated in the United States where knowledge on stroke and AMI symptoms was found to be lower in Spanish-speaking Hispanics compared with all other English-speaking racial groups.[13] Other American studies have also found longer delays to treatment for AMI for Hispanics than for non-Hispanic Caucasian

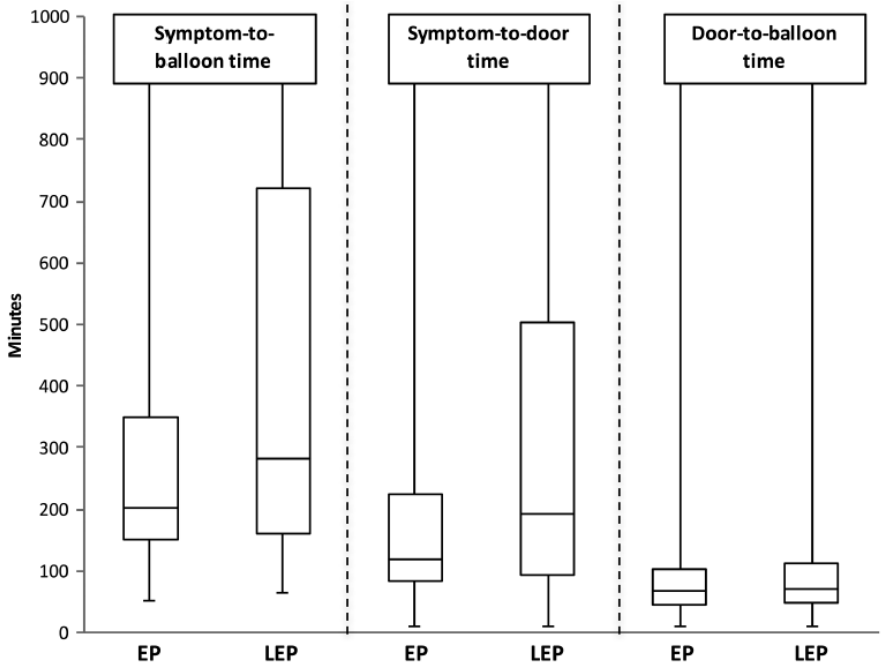

Figure 1 Comparison of times to reperfusion between English-proficient (EP) patients and patients with limited English proficiency (LEP).

Americans [14,15]. Potential barriers to seeking early treatment for LEP patients in our study may have been a reluctance to call for urgent ambulance services for cultural reasons, language barriers as well as concerns about cost. Strategies to improve knowledge in communities with a high proportion of LEP with targeted education are needed.

In this study the delays to presentation did not translate to an increased length of stay in LEP patients. Data from the CONCORDANCE registry comparing LEP and EP patients with ACS showed longer length of stay, as well as higher in-hospital and 6-month mortality in the LEP group.[9] Similarly an older Australian study comparing outcomes by English-speaking background also found a longer average length of stay in the non-English-speaking group; however, this study divided patients according to country of birth rather than language preference, which may have affected the results.[16] However, a large American study of MI patients by Grubbs *et al*. showed that length of stay and in-hospital mortality were not higher in LEP patients when adjusted for receipt of cardiac catheterisation or surgery.[17] STEMI care is much more streamlined than care of non-ST elevation ACS and our study only included those undergoing PCI which may explain the similarity between our results and those of Grubbs *et al*.[17] Streamlining of STEMI management with PCI and the use of clinical pathways with a checklist approach, such as those used across our health network, is likely to be an important contributor in ensuring that equal care is provided to all patients regardless of English-speaking capacity. Implementing similar care pathways in other areas of cardiology and healthcare in general may help to ensure LEP patients are not disadvantaged in their care.

There are several limitations to our study. There is no standardised tool to assess English proficiency status in the published literature and previous studies have used varying mechanisms to assess this ranging from using the language spoken in the patients' country of birth only, to using patients' self-reported language preference at different times in the hospital admission.[8,16] We performed our analysis based on patients' self-identification of their primary spoken language, which does not take into account their fluency, particularly in the EP group, which may affect patient care and understanding. In addition, similar to other studies, patients in our study were dichotomised into LEP and EP groups, whilst in reality English proficiency is much more of a continuum. As the registry did not collect data on ambulance utilisation, we were unable to compare this between the groups. The sample size in this study was also small and not adequately powered for assessing differences in mortality and MACE. As a result, we could not adequately adjust for baseline differences, including unmeasured variables, such as socio-economic status and educational level, which may have confounded the impact of English proficiency. The results therefore should be validated in a larger cohort in the future.

In conclusion, LEP was associated with significantly longer symptom-to-door time, but similar door-to-balloon times, in-hospital and 30-day mortality, compared with English-proficient patients in our study of STEMI patients undergoing primary PCI. Whilst it is reassuring that STEMI systems of care are robust such that LEP patients are not disadvantaged within the health system, these results highlight the need for better education about cardiovascular emergencies targeted to non-English-speaking communities.

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