Association of frailty status with the causes, characteristics and outcomes of patients with cardiovascular disease using electronic health record data.

Balamrit Singh Sokhal

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Declaration

This thesis was undertaken as part of an intercalated Master of Philosophy (MPhil) degree between the fourth and fifth year of the undergraduate medicine degree (MBChB) at Keele University. The idea for this thesis was conceived by me and Professor Mamas Mamas. I was responsible for the search strategy and systematic searches with support from Keele's systematic review team. The databases used in this thesis are comprised of routinely collected health record data from the United States and were provided by Professor Mamas Mamas. The statistical analyses presented in this thesis were planned by me with support from Dr Andrija Matetić and Professor Mamas Mamas. I was responsible for conducting the statistical analysis and interpreting the results with support from Dr Andrija Matetić. Overall supervision was provided by Dr Andrija Matetić, Professor Christian Mallen and Professor Mamas Mamas.

ਸੇਵਾ ਸੁਰਤਿ ਸਬਦਿ ਚਿਤੁ ਲਾਏ ||

Saevaa Surath Sabadh Chith Laaeae ||

Centre your awareness on seva and focus your consciousness on the Word of the Shabad.

Srī Gurū Granth Sāhib

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Contents

Abbreviations

ACC	American College of Cardiology
AHA	American Heart Association
AIDS	Acquired Immunodeficiency Syndrome
AMI	Acute Myocardial Infarction
AF	Atrial Fibrillation
AHRQ	Agency for Healthcare Research and Quality
AMED	Allied and Complementary Medicine Database
AOR	Adjusted Odds Ratio
BMI	Body Mass Index
CA	Cardiac Arrest
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CFS	Clinical Frailty Scale
CHD	Coronary Heart Disease
CI	Confidence Interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CVD	Cardiovascular Disease
DALY	Disability Adjusted Life Years
DVT	Deep Vein Thrombosis
EMBASE	Excerpta Medica Databases
ESC	European Society of Cardiology
FI	Frailty Index
FP	Frailty Phenotype
FRS	Framingham Risk Score
EHR	Electronic Health Record
GRACE	Global Registry for Acute Coronary Events
HCUP	Healthcare Cost and Utilisation Project
HF	Heart Failure
HFRS	Hospital Frailty Risk Score
ICD-10	International Classification of Diseases, Tenth Revision
IHD	Ischaemic Heart Disease
IQR	Interquartile Range

LDL	Low Density Lipoprotein
MACCE	Major Adverse Cerebrovascular and Cardiovascular Events
MEDLINE	Medical Literature Analysis and Retrieval System Online
NEDS	Nationwide Emergency Department Sample
NICE	National Institute for Health and Care Excellence
NIS	National Inpatient Sample
NSTEMI	Non ST-Elevation Acute myocardial infarction
NYHA	New York Heart Association
PCI	Percutaneous Coronary Intervention
PE	Pulmonary Embolism
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PVD	Peripheral Vascular Disease
SCORE	Systematic Coronary Risk Evaluation
SD	Standard Deviation
SPSS	Statistical Package for the Social Sciences
STEMI	ST-Elevation Acute myocardial infarction
SWIM	Synthesis Without Meta-analysis
TIA	Transient Ischaemic Attack
UK	United Kingdom
US	United States
USD	United States Dollar
VTE	Venous Thrombo-embolism
WHO	World Health Organisation
WOS	Web Of Science

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Abstract

Introduction

Cardiovascular disease (CVD) is the commonest cause of morbidity and mortality worldwide. Frailty is a clinical syndrome of physiological decline, resulting in adverse health outcomes. While the bidirectional relationship between CVD and frailty has been established, there is limited data on the contemporary association of frailty status with the causes, characteristics and outcomes of patients with CVD. This thesis aimed to investigate 1) the prevalence of frailty in CVD patients, 2) the clinical characteristics of frail CVD patients, 3) which CVD patients with frailty present with and 4) the outcomes of frail CVD patients.

Methods

Two studies were conducted. For the first study, CVD encounters from the 2016-2018 Nationwide Emergency Department (ED) Sample were stratified by their Hospital Frailty Risk Score (HFRS) into low risk (<5), intermediate risk (5-15) and high risk (>15). For the second study, CVD hospital admissions from the 2015-2019 National Inpatient Sample were stratified by their HFRS into low, intermediate and high risk. These samples were filtered by specific diagnoses: acute myocardial infarction, acute ischaemic stroke, atrial fibrillation (AF), heart failure, pulmonary embolism, acute haemorrhagic stroke and cardiac arrest.

Results

Over 20 million ED encounters and 16 million hospitalisations were identified. Frailty was present in a significant proportion of ED and hospital admissions for CVD. Increasing HFRS was associated with older age, female sex and increased comorbidities. Increasing frailty was associated with increased odds of mortality across most CVD. The largest effect size was observed in high HFRS patients diagnosed with AF for both studies (ED adjusted odds ratio (aOR) 27.14, 95% confidence interval (CI) 25.03-29.43 and in-hospital aOR 17.69, 95% CI 16.08-19.45 in-hospital compared to their low HFRS counterparts).

Conclusion

Patients have varying frailty risk according to CVD phenotype. Increased frailty is associated with increased all-cause mortality in patients with most CVD admissions. Knowledge of these trends is fundamental for the early recognition and optimal management of frailty in CVD patients.

1. Chapter 1: Introduction

1.1. Thesis Introduction

1.1.1. Burden of frailty

The average age of the population is increasing, which is largely related to advancements in healthcare, improvement in overall population health and the management of chronic conditions [1]. According to the World Health Organisation (WHO), in 2000, 600 million people were aged 60 years or above [2]. In 2018, this number increased to 1 billion and is expected to double to 2 billion by 2050 [2]. Age is strongly associated with frailty and therefore, with increasing numbers of the elderly population, the proportion of the fragile population is increasing [3, 4].

Frailty is conceptually defined as a syndrome of physiological decline resulting in an increased vulnerability to stress, leading to increased risk of adverse outcomes such as falls, hospitalisation and death [4]. A systematic review published in 2012 including 65,100 community-dwelling adults older than 65 years described the prevalence of overall frailty to be 10.7% [5]. Between 25% to 50% of people over 85 are estimated to be frail, with increased prevalence in females and in lower income countries [6-8]. However, investigating true estimates of the prevalence and burden of frailty can be difficult and strongly depends on the definition used and the population investigated [4]. Due to multiple causes and risk factors, there is an ongoing evolution in the contemporary understanding of frailty [4]. There is no agreed definition of frailty, yet there are multiple scoring systems to predict a person's frailty status [4]. Examples of validated tools include *Fried's* Frailty Phenotype (FP), *Rockwood's* Clinical Frailty Scale (CFS) and more recently *Gilbert's* Hospital Frailty Risk Score (HFRS) [9-11].

Frailty represents a significant healthcare burden [9, 12] and can impact on clinical outcomes, for example in comparison to patients without frailty, frail patients undergoing elective surgery are more likely to die (0.4% vs 0.0%) have an increased length of hospital stay (2.1 vs 0.8 days) and incur higher total costs ($3,129 vs $5,447) [13]. A study including 95,863 linked records of United Kingdom (UK) primary care patients concluded the extra annual cost to healthcare per patient to be £561 for patients with mild frailty, £1,208 for patients with moderate frailty and £2,108 for severely frail patients [14]. In total, this cost amounts to an additional £5.8 billion annually [14]. In comparison to non-frail patients, severely frail patients have an incidence risk ratio (IRR) of primary care consultations, emergency admission and inpatient days (IRR 1.52, 3.16 and 7.26 respectively) [14].

Pre-frailty is a state between non-frailty and frailty defined as having 3 of the 5 components of frailty present according to *Fried's* criteria (slowness, weight loss, weakness, low level of physical activity and exhaustion) [7]. Pre-frail patients have a higher chance of progressing to frailty and suffer worse outcomes compared to non-frail patients [7]. However, as with the definition of frailty, the definition of pre-frailty also varies in the literature [7]. Frailty is not an absolute fixed state as patients can transition between frail, pre-frail, and non-frail [7]. The prevalence of pre-frailty in a systematic review of 47,302 adults over 60 was 49.3% [7]. Frailty and pre-frailty carry a significant personal, societal, and financial impact, and there is a growing body of evidence that it can be reversed [15]. Therefore, it is important to identify at-risk groups.

1.1.2. Burden of cardiovascular disease

As with frailty, the numbers of patients living with cardiovascular disease (CVD) is increasing, particularly given the aging population and improved survivorship in patients with acute or chronic CVD [16]. CVD is the most common cause of morbidity and mortality worldwide [17].

The prevalence of CVD increased from 271 million in 1990 to 523 million in 2019, with deaths increasing from 12.1 million to 18.6 million in the same period [17]. CVD has significant implications for disability [17]. For ischaemic heart disease (IHD) in 2019, the total number of disability adjusted life years (DALY) increased to 182 million in 2019, with 9.14 million deaths and 197 million cases [17]. CVD tends to affect more males than females, and increasing age is a risk factor [17]. Other risk factors for CVD can be divided into metabolic, environmental, and behavioural [17]. Systolic blood pressure contributed to the greatest burden of CVD in 2019, followed by dietary risks, low-density lipoprotein (LDL) cholesterol levels, air pollution and high body mass index (BMI) [17].

Care for CVD incurs a substantial cost. From 1996 to 2016, spending on CVD care increased from $212 billion to $320 billion, with 54% covered by public insurance [18]. IHD was the largest cause of spending, followed by hypertension, hyperlipidaemia, and atrial fibrillation (AF) [18]. The cause of this expansion was attributed to several factors, such as increasing population, median age, and pharmaceutical prices [18]. In the UK, the cost of CVD was £29.1 billion in 2004 [19]. Therefore, both frailty and CVD are significant public health burdens that are identified by WHO as closely related target priorities.

The relationship between frailty and CVD is bidirectional [20]. CVD is associated with a three-fold increase in frailty and frailty is independently associated with an increased mortality from CVD [21, 22]. There are several simultaneous mechanisms that connect between frailty and CVD such as inflammation, concomitant risk factors and increased comorbidity burden [3]. However, it is unknown whether CVD admissions and in-hospital outcomes vary by frailty status. Information on the causes of admission for CVD in the frail population and the associated outcomes is vital to plan service around the needs of this key patient population.

Therefore, the aim of this thesis is to describe the cause of CVD admission, prevalence of frailty, clinical characteristics of frail patients, and outcomes of frail patients with CVD.

1.1.3. Thesis structure

This thesis consists of 4 further chapters (Chapters 2-5) in addition to this introductory chapter (Chapter 1). The rest of this chapter provides a summary of frailty and CVD as distinct entities. Chapter 2 summarises the current evidence of the use of the HFRS in patients with CVD with a systematic search of peer-reviewed articles on the topic of the relationship of frailty and ends with the thesis aims. Chapter 3 outlines the methods undertaken to investigate the thesis aims, including a description of the two datasets used: the Nationwide Emergency Department Sample (NEDS) and the NIS. Chapter 4 describes the results of each observational study included in this thesis. Finally, Chapter 5 provides a general discussion of the results, whilst summarising clinical implications and areas for future research. The general research questions addressed in this thesis are:

1) What is the prevalence of frailty in patients admitted with acute CVD?
2) What are the clinical characteristics of frail patients admitted with acute CVD?
3) What are the specific causes of acute CVD admissions in frail patients?
4) What are the outcomes following acute CVD admissions in frail patients?

1.2. Cardiovascular disease

1.2.1. Definition

CVD describes a variety of diseases that affect the heart and blood vessels [23]. Principally, CVD can be grouped into 6 categories defined by the WHO: coronary artery disease (CAD), cerebrovascular disease, peripheral vascular disease (PVD), rheumatic heart disease,

congenital heart disease and venous thromboembolism [17]. CAD can be used interchangeably with the term IHD and coronary heart disease (CHD), both terms include diseases that primarily affect the heart [24]. Cerebrovascular disease represents diseases which affect the vasculature of the brain. PVD covers pathologies which affect the vasculature which is not present in the heart, brain, or aorta [24]. Rheumatic heart disease consists of damage to the heart from rheumatic fever [24]. Congenital heart disease includes birth defects that affect the structure of the heart, with implications on the normal development and function of the heart [24]. Finally, venous thrombosis comprises of two diagnoses, deep vein thrombosis (DVT) and PE [24].

CVD is recognised as a global health priority [17]. Public health initiatives have focused on addressing the numerous risk factors for CVD, particularly behavioural and lifestyle interventions. This thesis will focus on 7 important conditions under the umbrella of CVD: acute myocardial infarction (AMI), acute ischaemic stroke, AF, heart failure (HF), pulmonary embolism (PE), cardiac arrest, and acute haemorrhagic stroke. Many CVD share the underlying pathophysiology of atherosclerosis, systemic inflammation and endothelial dysfunction. However, some of the CVD of interest in this thesis have their own discrete pathophysiology. Nevertheless, each CVD is associated with ageing and poor outcomes in the elderly.

1.2.2. Epidemiology

CVD is the leading cause of death worldwide [17]. The lifetime risk of CVD is 60% [25]. In 1990, the prevalence of CVD was 271 million with 12.1 million deaths [17]. By 2010, the global prevalence of CVD increased to 523 million, with 18.6 million deaths, while 85% of CVD deaths were due to AMI and stroke [17]. By 2025, deaths from CVD are estimated to rise to 25 million [17]. The global average life-expectancy is 78.8 years, yet one-third of CVD deaths occur before the age of 75 and DALY for IHD alone increased by 29 million from 1990

to 2010 [25, 26]. This demonstrates a substantial burden of CVD particularly in the elderly, which explains why CVD remains a global health priority [17].

Strategies for preventative care, and improvements in contemporary management have decreased mortality in developed countries [17]. Deaths in the UK between 1990 and 2013 decreased by 52% for CVD, 60% for CAD and 46% for stroke, while age-standardised mortality from CVD decreased by 70% from 1980 to 2013 [27]. Whilst mortality has decreased in developed countries, prevalence has increased, demonstrating the improved care and survivorship in patients with acute and chronic CVD [27]. However, 75% of CVD deaths occur in low-and-middle income countries despite the lower incidence of cardiovascular risk factors in these countries [24]. Mortality and an incidence of major adverse cerebrovascular and cardiovascular events (MACCE) in developing countries is still increasing [28]. Even in developed countries, socio-economic status is associated with increased risk of CVD and increased likelihood of adverse complications [29]. Data from less developed countries could be underestimated, as health statistics in these countries may not cover all areas or is incomplete or inaccurate [29]. Age-standardised mortality for CVD is 500 per 100,000 in Egypt, 400 per 100,000 in South Africa and 300 per 100,000 in China compared to 100 per 100,000 in Australia and the US [24]. Most CVD is preventable by addressing risk factors.

1.2.3. Risk factors

Despite temporal improvements in the care of CVD patients, the burden of risk factors is increasing, and therefore the prevalence of CVD is increasing [29]. Risk factors can be classified according to the control of the exposure and are therefore termed modifiable and non-modifiable **(Table** 1.1**)** [29]. The risk factors usually do not occur in isolation, with over 70% of at-risk individuals demonstrating more than 1 risk factor [30]. Both modifiable and non-modifiable risk factors should be considered in conjunction when assessing patients'

cardiovascular risk [17]. Overall, modifiable risk actors can be subclassified into metabolic, environmental, and behavioural [17].

Table 1.1 Risk factors of cardiovascular disease.

Modifiable	**Non-modifiable**
Metabolic	Age
Hypertension	Sex
Diabetes	Ethnicity
Hypercholesterolaemia	Genetics
Behavioural	Family history
Obesity	
Smoking	
Diet	
Physical activity	
Alcohol	
Environmental	
Socio-economic status	
Air pollution	
Temperature	

1.2.3.1. Modifiable risk factors

The most common modifiable risk factors are smoking, hypertension, diabetes, hypercholesterolaemia and obesity **(Table** 1.1**)** [29]. Therefore, these risk factors are often called standard modifiable risk factors. However, there are additional important risk factors that are difficult to control, such as kidney dysfunction or lung disease [17]. Examples of metabolic risk factors include high blood pressure, hypercholesterolaemia and increased BMI [17]. Hypertension is one of the leading CVD and a risk factor for other CVD. Its prevalence was up to 31.1% amongst the global adult population in 2010 [17, 31]. Furthermore, obesity is a common risk factor that potentiates both hypercholesterolaemia and diabetes [32]. The prevalence of obesity in 2008 was 33.8% and is expected to rise to 51% by 2030, with 11% of the population expected to be severely obese [32]. Comorbid CVD in patients with diabetes leads to poor outcomes, with over half of deaths in diabetics attributed to CVD [33]. The global prevalence of diagnosed diabetes in 2019 was 9.3% and is expected to rise to 10.2% by 2030

[34]. Hypercholesterolaemia and its association with CVD is primarily driven by high levels of low-density lipoprotein (LDL), leading to the atherosclerosis and endothelial dysfunction [35]. Metabolic risk factors can be affected in-part by behavioural risk factors. Examples of behavioural risk factors include diet, alcohol, and physical activity [17]. Increased exercise duration and vigour are independently associated with a decreased risk of CVD [29]. In contrast, increased fat and salt contents in diet lead to a higher likelihood of CVD [29]. Behavioural risk factors, whilst classically thought to only be controlled by the individual, can also be affected by environmental risk factors [17]. Examples of environmental risk factors include socio-economic status, air pollution and environmental temperature [17]. Unlike behavioural and physical risk factors, environmental risk factors, whilst modifiable, cannot be changed by the individual due to their population-wide effects [17]. Modifiable risk factors play a vital role to the development of CVD, with 1 modifiable risk factor leading to a 4-fold increase in adverse cardiovascular complications [30]. This risk increases to almost 60-fold in those with 5 modifiable risk factors, though this risk could differ depending on risk factor [30]. Small reductions in risk can lead to large reductions in adverse outcomes [30]. A 10% decrease in cholesterol and systolic blood pressure is associated with a 45% decrease in CVD incidence [30].

There is a growing body of evidence that a significant number of CVD complications occur in patients with no traditional modifiable risk factors [36, 37]. This population is associated with lower odds of invasive management and higher odds of adverse outcomes compared to patients with traditional modifiable risk factors [36-38].

1.2.3.2. Non-modifiable risk factors

Non-modifiable risk factors are another important vital aspect of CVD as those with no modifiable risk factors only have a 5% lower lifetime risk of CVD compared to those with

modifiable risk factors [39]. Non-modifiable risk factors include age, sex, ethnicity, family background and genetic factors **(Table** 1.1**)** [40]. The risk of CVD is increased by 70% for females and by 100% for males if one parent has CVD [41]. In the case of early-onset CVD, multiple genes have been implicated in its development due to their connection with atherosclerosis [41]. Ethnicity is a vital factor to the development and CVD and its complications [27]. The analysis of UK data showed that South Asians are 2 times more likely to develop CAD compared to the rest of the population, while African Caribbeans are more likely to develop hypertension [27]. In 2019, the incidence of CVD in the US was 77.2% for males and 78.2% for females aged 60-79, however in adults aged above 80, the incidence is 89.3% in males and 91.8% in females [42].

1.2.4. Risk assessment

To assess CVD risk, there are different risk scores worldwide. Global risk scoring systems such as the QRISK3 and Framingham Risk Score (FRS) calculate the risk of a MACCE in a given time period [43]. They are primarily used by primary care and consider comorbidities, modifiable risk factors and non-modifiable risk factors [43]. Risk stratification scores are fundamental to detect asymptomatic individuals with possible CVD, in order to timely prevent, recognise and treat CVD [43].

Due to population differences, different countries have different risk assessment tools to stratify their patients [44]. The FRS is preferred in Canada [45]. The updated Systematic Coronary Risk Evaluation (SCORE2) risk chart is advocated by the European Society of Cardiology (ESC) [46]. In the US, the joint American Heart Association (AHA)/ American College of Cardiology (ACC) Atherosclerotic CVD Risk Estimator tool is preferred [47]. According to the UK guidelines from the National Institute for Health and Care Excellence (NICE), patients over 40 should have their 10-year CVD risk regularly estimated using primary care electronic

health records (EHR) [48]. Patients with an estimated 10-year risk of 10% or more should be prioritised for a full clinical risk assessment [48]. QRISK3 is the preferred risk assessment tool of choice [48]. Components of QRISK3 include patient demographics such as age, sex and ethnicity, current health status including smoking status, systolic blood pressure, BMI, cholesterol levels and comorbidities such as AF, diabetes mellitus and renal disease [43, 49].

1.2.5. Cardiovascular diseases of interest

1.2.5.1. Acute myocardial infarction

AMI is defined as a disruption of blood flow to the myocardium commonly due to unstable plaque rupture, causing myocardial necrosis [39]. AMI is a the most severe form of CAD, which is responsible for more than a third of deaths in developed nations annually [50]. AMI can be sub-divided further depending on the aetiology [39]. Type 1 is the classical form of AMI and results from unstable plaque causing acute absolute coronary flow disturbance [39]. Type 2 AMI occur when the demand for oxygen by the myocardium is greater than the supply, with causes including coronary artery vasospasm, anaemia and unruptured atherosclerotic plaques, usually secondary to an underlying illness [39]. Type 3 AMI is sudden cardiac death in the absence of confirmed biomarker and electrocardiogram changes [39]. There are two sub-classifications of Type 4 AMI. Type 4a AMI is due to percutaneous coronary intervention [39]. Type 4b AMI is due to coronary stent thrombosis [39]. Finally, type 5 AMI is due to cardiac surgery, most commonly coronary artery bypass grafting (CABG) [39]. For the purposes of this thesis, type 1 AMI was the condition of interest.

AMI classically presents as chest pain that radiates to the left arm and neck, but the presentation varies with multiple symptoms of different intensity [39]. Investigations for AMI can be divided into non-invasive and invasive methods [39]. Non-invasive methods involve the use of

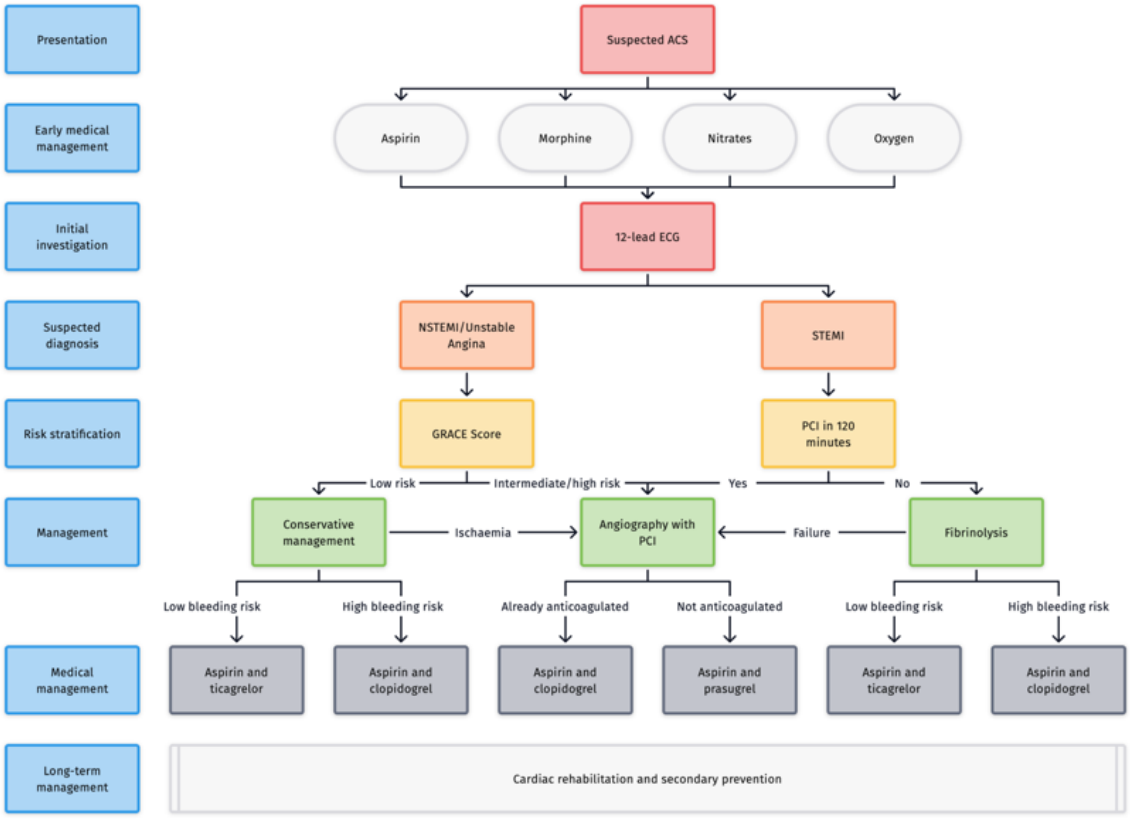
an electrocardiography and laboratory analysis [39]. Electrocardiographic results can be classified according to whether the ST segment is elevated or not elevated (STEMI and NSTEMI), and this usually informs the subsequent management strategy **(Figure** 1.1**)** [50]. Electrocardiograms have a 95% specificity (true negative) for AMI but only 30% sensitivity (true positive) [39]. Therefore, clinical assessment and electrocardiogram results are used in conjunction with laboratory analysis. Utilization of blood tests to detect biomarkers such as cardiac troponins is recommended in patients with suspicion for AMI [39]. Finally cardiac imaging in the form of coronary angiography can be used to the coronary anatomy and vessel patency and inform further management in the form of percutaneous coronary intervention (PCI) [51]. Importantly, an echocardiography can be used to assess the impact of CAD on heart function by detecting wall motion abnormalities, valve insufficiencies, and life-threatening complications like cardiac tamponade [50].

Two-thirds of patients with AMI over the age of 70 are admitted into hospital and 60% of deaths from AMI occur in this population [52]. Despite lifesaving interventions for AMI, the elderly population is still disproportionately adversely affected and are underrepresented in clinical trials. The 35-day mortality for AMI patients treated with thrombolysis has been reported to be 24.3% in patients aged over 75, compared to 3.4% in patients under 55 [52]. Patients aged over 75 have worse outcomes regardless of thrombolytic medication used, with 30 day mortality from alteplase at 19% and streptokinase at 21% compared to 4.4% and 5.5% for patients aged under 75 [52].

All AMI patients require immediate management in the form of high dose aspirin, and supportive medications if feasible, such as oxygen, opiates and sublingual nitro-glycerine [51]. Further medications and management are dependent on whether it is a STEMI or NSTEMI. Primary percutaneous coronary intervention is the gold-standard management of STEMI [51].

In the absence of primary PCI within 120 minutes, fibrinolysis should be performed [51]. For NSTEMI patients, a risk tool such as the Global Registry for Acute Coronary Events (GRACE) score is used to assess the timing of the invasive coronary angiography [51]. After the coronary angiography, the subsequent management is decided, and includes PCI, surgical revascularization, or medical therapy [51]. In the long term, the secondary prevention is critical and all cardiovascular risk factors are optimised [51].

Figure 1.1 Management of acute myocardial infarction.



1.2.5.2. Acute ischaemic stroke

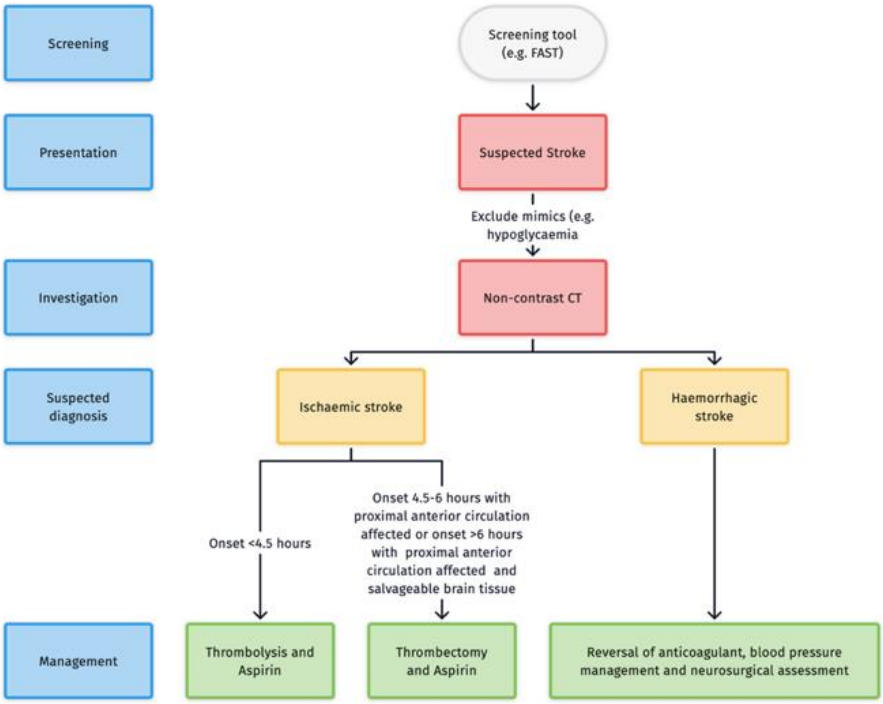
Acute ischaemic stroke is defined as an acute-onset, focal neurological deficit with evidence of damage to the brain parenchyma. About 85% of stroke are due to tissue ischaemia from arterial thrombosis and the remaining 15% are due to haemorrhage [42]. In 2018, there were

12.2 million incident strokes and 101 million prevalent strokes. Stroke is the leading cause of disability, with 50% of survivors being disabled, resulting in 143 million DALY in 2019 alone [53], and the second leading cause of death in the world (behind IHD), with an annual mortality rate of 5.5 million [54]. The overall lifetime risk of stroke is 1 in 6 for men and 1 in 5 for women [55]. Older age increases the risk stroke, with 70% of strokes occurring after the age of 65 [42]. In 2019, the age-standardised incidence of acute ischaemic stroke was 94.51 per 100,000 person years [53]. In the same period the death rate was 43.50 per 100,000 person years and the prevalence was 951 per 100,000 person years [53]. There are modifiable risk factors for stroke including hypertension, diabetes, smoking and AF and therefore, share similar risk factors to CVD [56]. Carotid artery stenosis is also a risk factor for stroke, with 2 of strokes occurring in patients with asymptomatic carotid stenosis [56].

Stroke has a myriad of manifestations but is commonly identified by a unilateral facial droop, contralateral loss of limb function and dysarthria [57]. Neuroimaging in the form of computed tomography is used to quickly identify stroke, as timing is crucial to management and long-term prognosis [57]. Magnetic resonance imaging can sometimes be used to further inform the anatomy and management [57]. Thrombolysis is considered within 4 hours and 30 minutes of onset and thrombectomy can be considered within 6 hours of onset, or up to 24 hours if there is still salvageable brain tissue on imaging **(**

Figure 1.2**)** [57].

Figure 1.2 Management of suspected stroke.

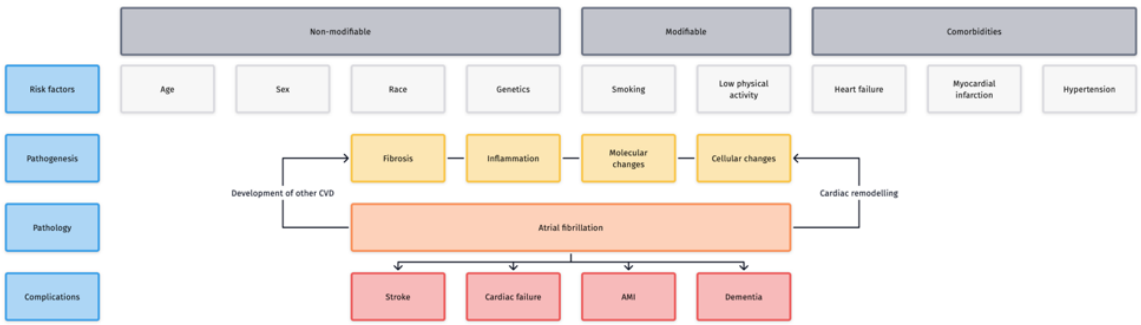


1.2.5.3. Atrial fibrillation

AF is the most common arrhythmia worldwide [58]. It is commonly defined as an irregularly irregular pulse caused by excitation of the atrium that results in irregular and dyssynchronous

atrial and ventricular contraction [58]. Symptoms drastically vary and it is detected using an electrocardiogram for routine health check-ups or consultations for palpitations or related health conditions [58]. AF is either caused by cardiac causes, extra-cardiac causes or idiopathic **(Figure** 1.3**)** [58]. Major cardiac causes include valvular heart disease, hypertension and left-atrial disease, all being more likely in the elderly [58]. Extra-cardiac causes include non-cardiac surgery, hyperthyroidism, alcohol, diabetes, and hypoxia, and therefore are related to other conditions [58]. Idiopathic AF generally occurs in younger patients where cardiac risk factors are absent, however there is no agreed underlying aetiology [58]. There are different types of AF: paroxysmal, persistent, and chronic [58]. Paroxysmal AF is defined as recurrent episodes of AF interspersed with sinus rhythm, lasting up to 7 days [58]. Persistent AF is defined as AF continuing beyond 7 days or until cardioversion [58]. Chronic AF is defined as AF resistant to cardioversion, or AF in which rhythm control methods were arbitrary abandoned [58]. The incidence of AF increases with age and is more commonly found in males [58]. The incidence of AF in patients aged 45-54, 44-64, 65-74, 75-84, and over 95 is 0.5, 1.1, 3.2, 6.2, 7.7 per 1000 persons respectively [58]. An ageing myocardium predisposes to alterations of the electrophysiology of the heart that lead to arrythmias such as AF [59]. The presence of AF leads to a higher risk of stroke, congestive cardiac failure, and AMI [58].

Figure 1.3 Pathogenesis of atrial fibrillation adapted from *Staerk et al. [58].*



The management of AF has several aims, to control heart rate, restore normal sinus rhythm, improve symptoms and prevent thromboembolic complications [60]. This is achieved by one of two methods depending on the presentation of the patient with AF: either rhythm or rate control. The primary aim of rhythm control is to restore normal sinus rhythm [60]. This is achieved pharmacologically with anti-arrhythmic medication, using electrical cardioversion or through percutaneous interventions (ablations) [60]. The primary aim of rate control is to control heart rate and manage symptoms [60]. This can be achieved with beta adrenoreceptor antagonists, calcium channel antagonists and digoxin [60]. To prevent further downstream recurrence and complications, patients are offered anticoagulation and lifestyle advice [60]. Anticoagulant medication is offered on a risk-benefit analysis, where the risk of stroke determines the need for anticoagulation, while the bleeding risk warrants the decrease of reversible bleeding risk factors [60]. This is usually performed by using risk stratification scores such as the CHA_2DS_2VASc score which predicts stroke risk following AF, and HASBLED score which predicts bleeding in AF **(Table** 1.2 **and Table** 1.3**)** [60]**.**

Table 1.2 Components of the CHA_2DS_2VASc score.

Variables	**Score**
Congestive HF	1
Hypertension	1
Age >75	2
Age 64-75	1
Diabetes	1
Stroke/TIA/Thrombo-embolism	2
Vascular Disease	1
Female Sex	1

Table 1.3 Components of the HASBLED score.

Variables	**Score**
Hypertension	1
Abnormal renal/liver function	1 or 2
Stroke history	1
Bleeding tendency or bleeding predisposition	1
Labile International Normalised Ratio	1
Age >65	1

Medications predisposing bleeding	1
Alcohol use	1

1.2.5.4. Heart failure

HF is a clinical syndrome manifesting as the result of structural and functional defects which impair ventricular filling or ejection of blood, affecting up to 2% of the adult population [61]. Most commonly, the cause of HF is left ventricular myocardial dysfunction, however defects can occur anywhere in the myocardium, pericardium, or endocardium [61]. HF is classified according to the site of impairment into left ventricular, right ventricular, or biventricular, and then further sub-classified according to the ejection fraction in preserved, mid-range or reduced [61]. HF can present with shortness of breath, orthopnoea and paroxysmal nocturnal dyspnoea, and raised brain natriuretic peptide levels [61]. Therefore HF causes significant impairment to daily activities [61]. The functional status of patients is classified according to the New York Heart Association (NYHA) as class 1 (no functional impairment) to class 4 (severe functional impairment) [62]. The prognosis is poor, with 50% of NYHA class 4 HF patients developing fatal event within 1 year of diagnosis [62].

5.7 million people in the US have HF, which is predicted to rise to 8 million by 2030 [63]. HF affects more men than women and its prevalence increase with age [59, 63]. As mentioned, age is a significant risk factor for HF due to increased vulnerability to stress and chronic inflammation [59]. Ageing is associated with an increased incidence of left ventricular hypertrophy, decreased left ventricular diastolic function, left atrial dilation, decline in exercise tolerance, and increased incidence of AF [59]. All have a direct impact on the morphology and residual function of the heart [59]. Increasing age is associated with an increased heart mass to volume ratio of 5 mg/ml/year as well as a fall in stroke volume by 0.4 ml/year [59]. All factors

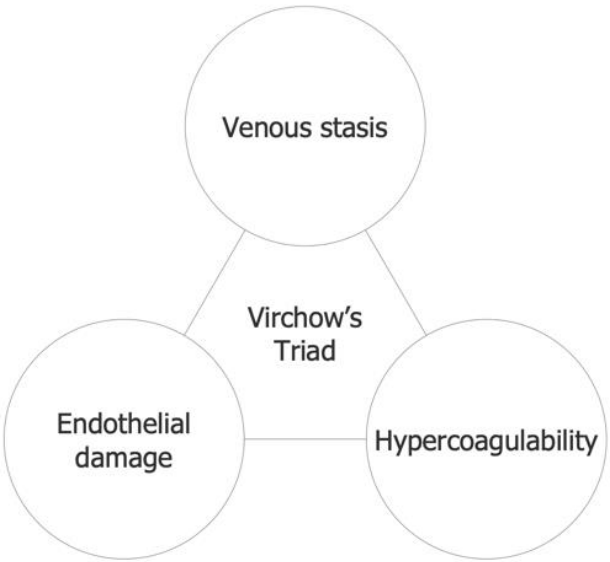
could lead to a reduction in stroke volume and compliance, resulting in a lower cardiac output [59].

1.2.5.5. Pulmonary embolism

PE is defined as a venous thrombo-embolism (VTE) that travels to and occludes the arteries of the lung [64]. In the United States (US), the estimated incidence of PE is 65 per 100,000 however the true value is thought to be higher as PE can remain undiagnosed or diagnosed at autopsy. Up to 10% of in-hospital deaths are a direct result of PE [64]. Mortality from PE is dependent on the degree of obstruction and haemodynamic compromise [65, 66]. Massive PE, defined as a PE causing systematic arterial hypotension due significant obstruction of the pulmonary vasculature, have a reported mortality of 25% to 65%, yet this risk reduces to 3% to 15% for sub-massive PE and reduces to less than 1% in patients with low-risk PE, normal heart function and anticoagulation [65, 66].

Risk factors for VTE can be classified according to Virchow's Triad of blood stasis, endothelial damage and hypercoagulability **(Figure** 1.4**)** [64]. These factors can also be divided into inherited factors (e.g. Factor V Leiden, protein C and protein S deficiency) and acquired factors (e.g. trauma, surgery and malignancy) [64]. Atherosclerosis from CVD is implicated to increase the VTE risk due to hypercoagulability and endothelial dysfunction [67]. However, shared risk factors such as smoking, obesity and age could equally contribute [65]. The risk of VTE increases with age, with patients over the age of 70 being 3 times more likely to develop VTE compared to those aged 45 to 69 [64]. The proposed mechanism is an imbalance between anticoagulants and procoagulants, resulting in a hypercoagulable state, generally starting in the 4^{th} and 5^{th} decade of life [64]. Furthermore, age increases risk of other factors such as decreased mobility, obesity, comorbidities and malignancy [64].

Figure 1.4 Virchow's Triad.



1.2.5.6. Cardiac arrest

Cardiac arrest is a complication from an acute event, where there is loss of cardiac activity and systemic circulation, resulting in a cell damage and oedema formation [68]. The reported incidence and outcomes of cardiac arrest varies greatly per study as metrics to identify cardiac arrest varies by database, population, and management of cardiac arrest between countries. Cardiac arrest can either occur in-hospital or out of hospital. Out of hospital cardiac arrest has an annual incidence of 350,000 in the US, and is associated with poor outcomes, with approximately 12% of patients surviving to discharge. In-hospital cardiac arrest has an annual incidence of 290,000 in the US, amounting to 7 cardiac arrests per 1000 admissions. In-hospital cardiac arrest has relatively better outcomes, yet only 25% of patients survive to discharge, generally attributed to the immediate provision of basic and advanced life support. However, despite being discharged, 15% of patients still have an unfavourable neurological outcome. Cardiac arrest is more likely in patients around 65 years and in men (60%) [69]. Cardiac arrest can also occur in younger, athletic patients, with 1 in 23,000 to 1 in 200,000 athletes per year experiencing cardiac arrest [68]. Cardiac arrest in younger patients is commonly due to underlying structural or arrhythmogenic heart disease, that manifests on exertion [68]. About

80% of out of hospital cardiac arrest have underlying cardiac cause with 80% of patients who experience sudden cardiac death having evidence of underlying CAD [68]. The prevalence of CAD and sudden cardiac death increases with age [68]. Older age is associated with decreased survival following cardiac arrest [69]. About 59% of 65-year-olds discharged following cardiac arrest survive at 1 year, with 34% not requiring readmission [69]. In-hospital cardiac arrest are mostly due to either cardiac (50-60%) or respiratory (15-40%) causes [69]. The concept of 4H's and 4T's have been identified as the main reversible causes of cardiac arrests (**Table** 1.4) [69]. The two strongest factors to determine prognosis of cardiac arrest is the duration of cardiac arrest and the presenting rhythm [69].

Table 1.4 Reversible causes of cardiac arrest.

4H's	**4T's**
Hypoxia	Tension pneumothorax
Hypovolaemia	Tamponade
Hypothermia	Toxins
Hyper/Hypokalaemia and -calcaemia	Thrombo-embolus

1.2.5.7. Acute haemorrhagic stroke

Acute haemorrhagic stroke is defined as a bleeding into the brain due to a ruptured blood vessel, responsible for 15% of all strokes [70]. It is an umbrella term for intracerebral haemorrhage and subarachnoid haemorrhage [70]. It shares similar clinical features to acute ischaemic stroke, but can and should be differentiated using imaging methods [71]. Acute haemorrhagic stroke is most commonly caused by uncontrolled hypertension, cerebral amyloid angiopathy, aneurysms and head injuries [70]. The risk of acute haemorrhagic stroke increases with age, with an incidence ratio of 9.6 (CI 6.6-13.9) for patients aged 85 years and older compared to patients aged 45-54 [72]. Acute haemorrhagic stroke is associated with significant morbidity

and mortality [72]. Independency rates from acute haemorrhagic stroke is between 12% and 39% and overall mortality rate is between 30% and 50% [72]. The trends in incidence and adverse outcomes have not changed significantly over time [72]. Acute haemorrhagic stroke progression is characterised by neurological dysfunction and is caused by a variety of factors: haematoma expansion, peri-haematoma oedema, intraventricular haemorrhage, and inflammation [71]. Haematoma expansion is defined as an increase of haemorrhage by 33% from the baseline, or a volume increase by 1.4 times or 12.5 cm^3 [71]. Haematoma expansion occurs in 12-40% of all acute haemorrhagic stroke patients [71]. Intraventricular progression of the haemorrhage occurs in 20-55% of patients and is associated with a more severe functional decline and a higher mortality rate, when adjusting for other causes [71]. Perihematomal oedema occurs within the first day of spontaneous haemorrhage and peaks after 5 days, potentially causing mass effect [71]. Finally, an acute inflammatory response is associated with deterioration of acute haemorrhagic stroke and is a predictor for worse short and long-term outcomes [71].

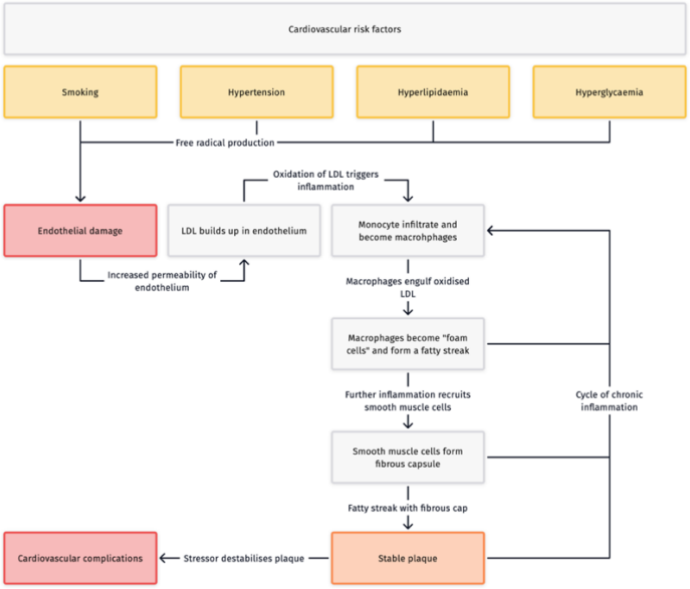
1.2.6. Pathophysiology of the cardiovascular diseases of interest

The most common underlying mechanism of CVD is atherosclerosis caused by modifiable and non-modifiable risk factors **(Figure** 1.5**)** [35]. Atherosclerosis commences with endothelial dysfunction due to damage from hypertension, hyperglycaemia, hypercholesterolaemia and smoking [35]. Oxidative stress and the presence of reactive oxygen species damage the endothelium [35]. Activated endothelium upregulates adhesion proteins, and therefore is more permeable to immune cell and low-density lipoprotein (LDL) infiltration [35]. LDL builds up in the endothelial space where it undergoes oxidation into lipids through its interaction with reactive oxygen species [35]. LDL has a higher propensity to accumulate in vascular endothelium compared to high density lipoprotein due to a charged interaction between LDL

and the matrix proteoglycans [35]. Oxidation triggers chronic inflammation, promoting monocyte migration into the tunica intima [35]. Monocytes are then activated to become macrophages, which releases pro-inflammatory cytokines and chemokines [35]. Pro-inflammatory cytokines recruit smooth muscle cells and induce proliferation [28]. Oxidised LDL is up taken by macrophages and become filled with lipid, becoming "foam cells" [35]. Over many years, foam cells accumulate to become an atheroma [28]. Foam cells continue to release pro-inflammatory cytokines, inducing migration of smooth muscle cells to form a fibrous capsule in order to stabilise the lesion [35]. The intimal thickening leads to narrowing of the blood vessel, however this does not initially reduce blood flow [28]. Coronary arteries can remodel (Glagov phenomenon) to preserve the cross-sectional area to maintain blood supply to the myocardium, and therefore, no symptoms are produced [28]. Over many years, the chronic inflammatory process further narrows blood vessels, reducing downstream blood flow [28]. This process does not progress linearly [35]. The lesion undergoes neo-vascularisation, remodelling and in some instances can regress [35]. Stable plaques have lower levels of inflammation and higher levels of smooth muscle cell survival, creating a stronger capsule [35]. Sudden bursts of inflammatory activity, for example due to continued insult and deposition of dead cells, causes the fibrous capsule to become weaker leading to an unstable plaque and subsequent thrombosis and adverse cardiovascular events [28]. Inflammatory cells produce pro-apoptotic cytokines and chemokines which inhibit smooth muscle cells and degrade the collagen produced by smooth muscle cells [35].

Modifiable risk factors initiate the process of atherosclerosis, and non-modifiable risk factors generally are responsible for driving the process further through a variety of mechanisms [73]. Age has a significant effect on inflammatory process underlying atheroma formation as it is associated with immune dysregulation, which increases the circulating pro-inflammatory cytokines [73]. Therefore, age is a strong risk factor for CVD.

Figure 1.5 Process of atherosclerosis.



1.3. Frailty

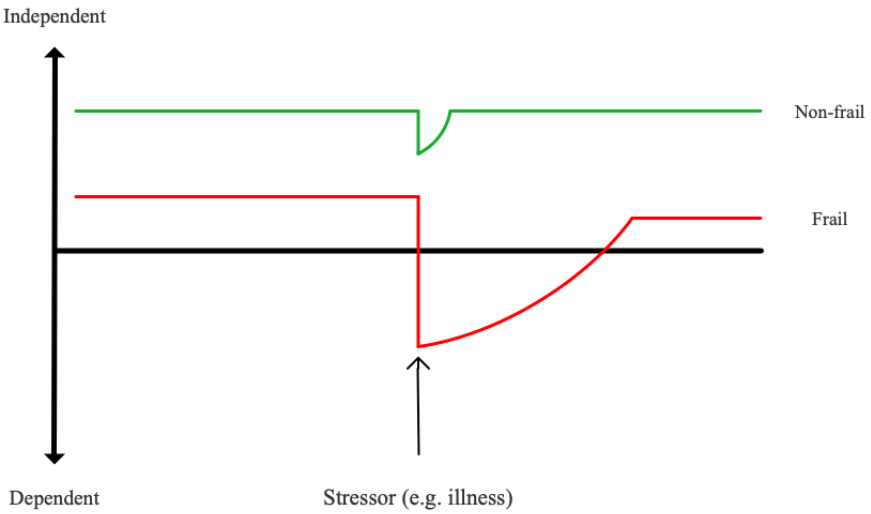
1.3.1. Definition

Broadly, frailty can be defined a clinical syndrome of physical decline and decreased functional capacity across multiple organ systems resulting in an increased vulnerability to stress **(**

Figure 1.6**)** [4]. Frailty is associated with adverse biological, physiological, and sociological health outcomes [74]. It is classified as a geriatric syndrome and therefore is most strongly associated with increasing age [74]. There are many mechanisms implicated in the development of frailty, however these are poorly understood [4]. Contemporary research has led to developments and improved care of elderly patients and by extension, frail patients [4]. However, there is no single agreed clinical definition or assessment of frailty [4]. Definitions

can be classified according to the theoretical models or the established research models that exist in the literature [75]. There are two major models of frailty, the Phenotype Model, and the Cumulative Deficit Model [9, 76]. The Phenotype Model is based on physical characteristics of patients such as muscle strength, exhaustion, and low energy, giving rise to the term 'physical frailty' [9]. A major determinant to physical frailty alongside age is sarcopenia, defined as loss of skeletal muscle function [9]. The Cumulative Deficit Model describes frailty as a collection of different insults to the body varying from symptoms like hearing loss to diseases such as dementia [11]. Frailty is preceded by pre-frailty, which is an early, reversible state before frailty [4]. Pre-frail patients are more likely to suffer adverse health complications compared to non-frail patients. Pre-frail patients can be identified using the same assessment tools as used to assess frailty [4].

Figure 1.6 Response to acute stressors in frail patients versus non-frail patients from *Clegg et al* [1].



1.3.2. Epidemiology

The reported prevalence of frailty between studies varies and is dependent on the definition and the measurement system used [77]. A systematic review of the global prevalence of frailty found frailty to be present in 12% of people aged over 50 using physical models and 24% using deficit models [77]. The prevalence of pre-frailty was 46% using the physical model and 49% using the deficit model in the same population [77]. The prevalence of frailty was highest in Africa and lowest in Europe [77]. Another systematic review described the prevalence of frailty among community-dwelling older adults to be between 4.0% and 59.1% [5]. A meta-analysis of 46 observational studies of 120,000 non-frail patients found the incidence of frailty to be between 43-150 per 1000 person-years [6]. Pre-frail patients had higher risk of frailty than non-frail patients (62.7 versus 12.0 cases per 1000 person-years for pre-frail and non-frail patients, respectively) [6]. The development of frailty is dependent on many factors including age, sex, socioeconomic status, and comorbidities [4].

Age is a strong risk factor of frailty, with age over 50 being substantially associated with increased frailty risk (8-14% of 50–59-year-olds, 29-34% aged 80-89) [78]. Female sex is also a risk factor for frailty [6] . A systematic review of community dwelling older adults found frailty incidence was higher in females compared to males (44.8 versus 24.3 cases per 1000 person-years for females and males respectively) [6]. The highest incidence of frailty is observed in selected populations such as cancer patients (42% for frailty and 43% for pre-frailty), HF patients (44.5%), end-stage renal disease patients (36.8%) and patients with depression (40.4%) [79].

Numerous studies have reported a relationship between frailty and adverse outcomes [9, 76, 80, 81]. In summary, frailty is a predictor to incident falls, worsened mobility, disability, incident hospitalisation and death [9]. Increased death risk persists after 5 years for mildly frail

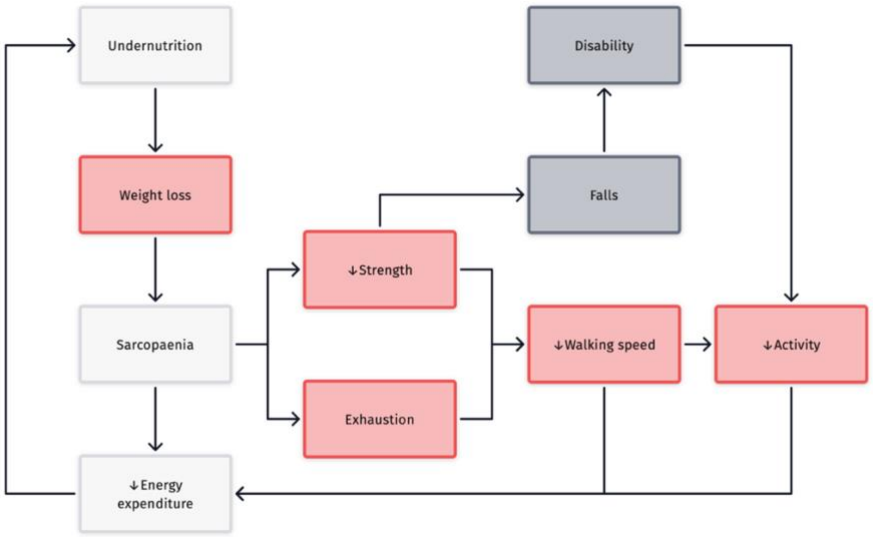
patients (odds ratio (OR) 4.82 (95% CI 3.74 to 6.21) and highly frail patients (OR 7.34 95% CI 4.7 to 11.38) [76]. Female sex carries a 6 times increased risk of death and 10 times increased risk of disability and nursing home entry compared to males [80]. Frail patients have increased odds of 2 or more falls within a year, with the risk increased in females [81].

1.3.3. Risk factors

Research on frailty mainly focuses on physical activity and hence, health interventions focus on increasing exercise amongst at risk groups [82]. However, frailty has numerous risk factors from genetics to age and comorbidities [82]. These factors can be divided into sociodemographic, physical, biological, lifestyle and psychological [82]. Sociodemographic factors include increasing age, female sex, black or Hispanic ethnic background, low income, and low education level [82]. Significant physical risk factors include increased BMI, decreased activities of daily living, and decreased functional status [82]. Biological factors include increased serum C-reactive protein, uric acid, and albumin, and decreased free testosterone and sex hormone binding globulin [82]. There has been no significant association found in relation to immunological biomarkers of frailty such as erythrocyte sedimentation rate, neutrophil count, thyroid hormone, and interleukin levels [82]. Significant lifestyle factors include diet and increased smoking and alcohol intake [82]. A Mediterranean diet is disputed as a protector of frailty, with some studies reporting a lower likelihood of frailty and some reporting no association [82]. The association between alcohol and smoking and frailty is also mixed [82]. Smoking has either been found to have no association or a small positive association whereas alcohol has been found to have a negative association with frailty [82]. Higher protein, fruit and vegetable consumption is associated with a lower risk of frailty [82]. Finally, significant psychological factors include depression, cognitive function, and higher affect [82]. No association have been found between frailty and emotional support and

medication use [82]. Risk factors for frailty are related and are thought to result in sarcopenia and reduced total energy expenditure leading to deconditioning and dependency [83]. This leads to what has been described as a self-perpetuating cycle of events, as outlined in the Women's Health and Aging Study II **(Figure** 1.7**)** [83].

Figure 1.7 Cycle of Frailty adapted from *Xue et al.* [83].

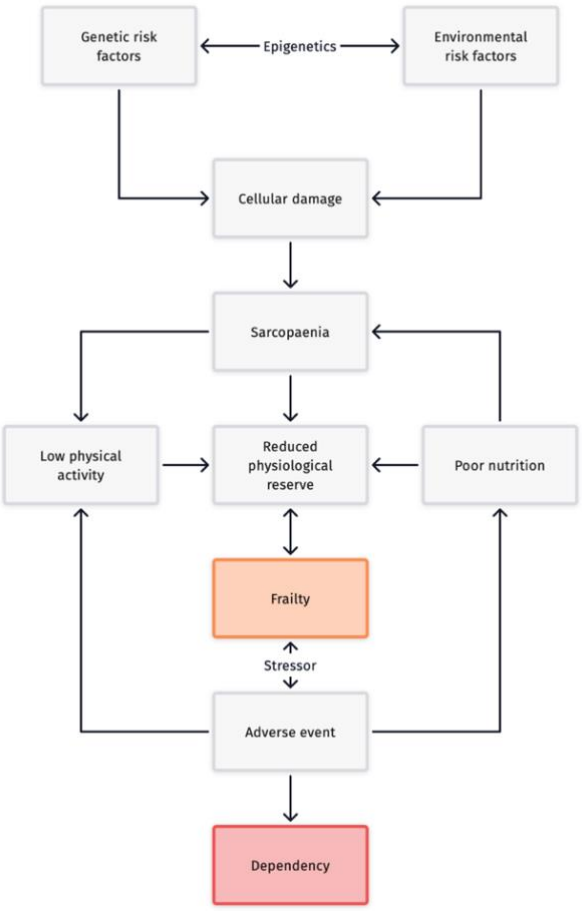


1.3.4. Pathophysiology

1.3.4.1. Inflammation

The pathophysiology of frailty is a debated topic. Whilst there are established hypotheses behind frailty, research is still in its early stages in gaining a definite understanding of the processes involved [74]. Generally it is agreed that frailty can a result of loss of the homeostatic balance of the body, rather than a distinct pathology in itself [74]. The proposed mechanism is chronic inflammation that shares direct and indirect pathophysiological processes that primarily affect the cardiovascular, endocrine, haematological, and musculoskeletal systems **(Figure** 1.8**)** [74].

Figure 1.8 Pathophysiology of frailty, adapted and modified from *Clegg et al.* [1].



Chronic inflammation has been identified as the key underlying mechanism driving frailty. Inflammatory markers such as neopterin, interleukin 6 (IL6), tumour necrosis factor alpha (TNFα), and C-reactive protein are increased in patients with frailty [74]. This is likely due to a myriad of causes including ageing, genetics, lifestyle, environment, and diseases [74]. These inflammatory markers recruit monocytes and macrophages, which in turn release further inflammatory markers, inducing advanced inflammation leading to decreased muscle mass, strength and power [74]. This leads to chronic inflammation, underpinning the process of frailty [74].

Clinically, immune dysregulation manifests as an increased or upper range of normal white blood cell count and increased neutrophils and monocytes [74]. This leads to increased counts

of differentiated pro-inflammatory T-cells [74]. Ageing decreases the efficiency of the immune system leading to an increased susceptibility to comorbidities such as cardiovascular disease, dementia, cancer and diabetes [84]. These diseases also either cause or are underpinned by a chronic inflammatory process, accelerating the disease processes but also the progression to frailty [84].

1.3.4.2. Endocrine system and sarcopenia

Multiple hormones have been implicated in the process of frailty through their contribution to sarcopenia, in particular sex hormones, vitamin D, metabolic hormones and growth hormone [85]. Lower levels of free testosterone in men and oestrogen in women and Insulin-like Growth Factor 1 lead to decreased muscle mass and strength, leading to sarcopenia [74]. Chronic inflammation and chronic disease, both more prevalent in the elderly, accelerate this process, inciting the cycle of frailty [4].

As many definitions of frailty focus on the physical performance of patients, the musculoskeletal system plays a vital role in decreasing the likelihood of progression to frailty [74]. Sarcopenia is one of the most important contributors to frailty [74]. Other direct relationships include osteopenia and osteoporosis [74]. Sarcopenia is defined as a loss of muscle strength and mass after the age of 50 [74]. It is caused by changes in type 1 muscle fibres, malnutrition, hormonal imbalance and reduced physical activity [74]. More contemporary studies are targeting sarcopenia to prevent or delay frailty, given its impact on the overall health [74].

1.3.5. Assessment tools

1.3.5.1. Rockwood's Clinical Frailty Scale

Frailty has been objectively measured using a variety of methods **(**

Table 1.5**)**. Frailty has been operationalised as a combination of specific features, which whilst precise, can neglect individuals whom do not possess the specific combination of factors required to match the rules-based definition [11]. These operationalised components have been combined with clinical judgement from history taking and clinical examination to increase detection, however this is subject to user bias from the clinician [74]. Finally, frailty has also been modelled as a sum of impairments, which can strongly predict future outcomes [74]. However, lack of routinely collected data and detailed patient history would prevent from using these assessment methods. There are three widely used models to quantify frailty risk: *Rockwood's* CFS, *Fried's* FP, and more recently *Gilbert's* Hospital Frailty Risk Score (HFRS) [9-11]. The CFS uses the operational model and combines it with clinical assessment [11, 76]. The FP model developed by *Fried et al.* uses five operationalised criteria: slowness, weight loss, weakness, low level of physical activity and exhaustion [74]. The HFRS quantifies frailty by the number of diagnoses from routinely collected health record data [10].

Table 1.5 Measurements of frailty.

Measurement	**Model**
HFRS	Cumulative deficit
Frailty Index	Cumulative deficit
Frailty Phenotype	Operational
Frailty Scale	Clinical assessment
Edmonton Frail Scale	Operational & cumulative deficit
Survey of Health Ageing and Retirement in Europe Frailty Index	Operational
Green Score	Operational
Fatigue, Resistance, Ambulation, Illness and Loss of Weight Score	Operational
Tilburg Frailty Indicator	Operational
Gait speed	Operational
Short Physical Performance Battery	Operational
Grip strength	Operational
Gait speed	Operational

Rockwood et al. proposed and operation classification of frailty using a 7 category CFS [11]. Therefore, the CFS sought to measure frailty from clinical judgement [76]. The Canadian Study of Health and Ageing, a 5-year prospective cohort study from 1991 with 10,263 participants aged 65 and above, was used [76]. The original cohort study was designed to describe the epidemiology of cognitive impairment in Canadians [76]. The study gathered information on baseline demographics and clinical characteristics from clinical examination [76]. They firstly developed a rule-based definition of frailty using only clinical examination findings [76]. Following this, their cumulative deficit model with 70 components termed the Frailty Index (FI) was developed, which is popular in contemporary assessments of frailty [76]. However, each had their own distinct limitations that were outlined in above [76]. The CFS included 82 variables ranging from signs, symptoms, laboratory values, diseases and disabilities [76]. This was validated using 2,305 elderly participants without dementia who participated in the 2nd stage of the Canadian Study of Health and Ageing [11]. This was then compared against other scores such as the Modified Mini-Mental State Examination and Cumulative Illness Rating Scale [11]. The 7 categories were: very fit (1); well without active disease (2); well with treated active disease (3); apparently vulnerable (4); mildly frail (5); moderately frail (6); and severely frail (7) **(Table** 1.6**)** [11]. Finally, for the 3rd stage of the Canadian Study of Health and Ageing, the CFS was validated by a 5-year follow up of the 1,299 participants that were still alive since the 2nd stage of the study. At the end of the 2nd stage of the study, a clinician assigned a number from the CFS to each patient [11]. At the end of the 3rd stage, this was repeated, but with the addition of a multidisciplinary team [11].

Table 1.6 Categories of Rockwood's Clinical Frailty Scale, adapted from *Rockwood et al* [11].

Category	Name	Features
1	Very fit	Robust and active.
2	Well without active disease	Without disease, but less fit than category 1.
3	Well with treated active disease	Active comorbidities but controlled by treatment.

4	Vulnerable	Active comorbidities not controlled with treatment.
5	Mildly frail	Dependent on others for activities of daily living.
6	Moderately frail	Dependent on others for most activities of daily living.
7	Severely frail	Complete dependence or terminally ill.

Participants with increasing CFS score were more likely to be older and female and have more comorbidities such as cognitive impairment, incontinence and impaired mobility [11]. Increased CFS category is associated with decreased probability of survival and increased probability of institutionalised care over a period of 70 months (area under curve 0.70 for mortality and 0.75 for institutionalisation) [11]. More specifically, a 1-category-increase was associated with an increased risk of death (21.2% 95% CI 12.5-30.6%) [11].

There are several strengths and weaknesses to the CFS. Strengths include its use of a clinical assessment and components such as comorbidity, disability, and cognitive impairment, which is overall, less reliant on the physical frailty [11]. Furthermore, the CFS demonstrated relatively strong predictive abilities when compared to other frailty measurement systems available at the time of the study [11]. Limitations from this study include the overrepresentation of participants with cognitive impairment in the derivation cohort, potentially leading to underestimation of frailty in those without cognitive impairment [11]. Furthermore, given the CFS is partially based on clinical assessment from a clinician, it is susceptible to user bias [11]. Some clinicians may or may not recognise aspects of the presentations of patients that may warrant a robust assessment using the CFS [11]. This could lead to variability in its application [11].

1.3.5.2. Fried's Frailty Phenotype

Fried et al. proposed a classification of frailty based on 5 phenotypes included in the cycle of frailty that were hypothesised to account for the main clinical presentations of frailty:

sarcopenia; weakness; exhaustion; slowness; and low activity [9]. Each phenotype was operationalised and their prevalence, incidence, and validity for predicting adverse outcomes were investigated using the unrelated Cardiovascular Health Study **(Table** 1.7**)** [9]. The Cardiovascular Health Study included 5,201 Americans in 1989-90 from 1992-93, and later expanded to include 687 African Americans [9]. The study by *Fried et al.* included 5,317 participants aged 65 years and over [9]. All patients received similar baseline evaluations [9]. This included interviews ascertaining demographics, self-reported comorbidities, medications, and health status. Cardiovascular specific characteristics were verified by medication and baseline electrocardiogram, echocardiogram, and ankle-brachial index [9]. Follow up occurred in the form of annual examinations, telephone visits and simple surveillance of complications such as hospitalisations, falls and mortality [9]. Frailty was defined as "a clinical syndrome where 3 or more of domains were present" whereas pre-frailty was defined by the presence of 1 or 2 of the domains [9]. Sarcopenia was assessed as: weight loss in the preceding year; weakness defined as grip strength measured by a dynamometer; exhaustion measured by the Centre for Epidemiological Studies Depression Scale; slowness defined as time to walk 15 feet; and low activity defined by the Minnesota Leisure Time Activity Questionnaire. Each component was adjusted for relevant characteristics that were obtained from the baseline assessment [9].

Table 1.7 Components of the Frailty Phenotype adapted from *Fried et al.* [9].

Category	Name	Features
1	Sarcopenia	Unintentional weight loss of ≥5% of body weight in prior year.
2	Weakness	Strength of grip in the lowest 20% adjusted for age and BMI.
3	Exhaustion	Self-reported based on Centre for Epidemiological Studies Depression Scale.
4	Slowness	Time to walk 15 feet in lowest 20% adjusted for age and height.

5	Low activity	Self-reported kilocalories expended per week in lowest 25% by sex.

Frailty was more frequently observed in participants who were older, female, African American and in those with higher rates of chronic comorbidities and disability [9]. About 7% of the initial cohort and 12% of the African American cohort were defined as frail, with increasing prevalence at each 5-year age interval, and double rates in females [9]. The incidence of frailty was 7% for year 0-3 and 3-7 [9]. Frail patients had higher rates of falls, hospitalisations and death. Pre-frail patients also had an increased risk of both adverse outcomes and progression to frailty compared to non-frail patients [9].

There were several strengths and limitations of this classification of frailty. A major strength included the clear division between frailty, comorbidity and disability, as these entities can overlap, despite commonly being used interchangeably [9]. Frailty has been defined previously. Disability is defined as dependency for an activity of daily living. Medically it is diagnosed from self-reported activities [9]. About 20-30% of community dwelling adults aged 70 or over reported physical disability, most commonly for mobility [9]. Comorbidity is medically defined as the diagnoses of two or more medical conditions for the same individual. Comorbidities tend to increase with age, with around 70% of the US population above 80 years of age reporting 2 or more diseases [86]. This study featured components that rarely overlap with measures of disability and comorbidity, ensuring that frailty is diagnosed as its own clinical syndrome [9]. Another strength of this study includes the assessment of frailty using relatively inexpensive and straightforward methods [9]. This study's main limitation is that only phenotypes collected routinely in the original cohort were subsequently used in further studies [9]. Therefore, other important factors of frailty, such as medical history, could be underrepresented [9]. Another limitation results from being a questionnaire-based study that is subject to recall bias [9]. Finally, whilst an assessment would not be intensive, it does not

provide the depth of information of scores that utilise routinely collected healthcare, which can cover a wider range of demographic information and comorbidities [9]. Therefore, this score relies on the decision of the clinician as to whether a patient requires assessment, meaning frail patients requiring assessment could be missed due to user bias [9].

1.3.5.3. Gilbert's Hospital Frailty Risk Score

Gilbert et al. developed the Hospital Frailty Risk Score (HFRS) to establish whether elderly patients at risk of adverse outcomes could be identified using routinely collected healthcare data, without the need for a manual assessment [10]. The study followed a 3-step process to create the HFRS [10]. First, a cluster analysis of a group of elderly patients admitted to hospital with characteristics of frailty was used to identify characteristics associated with frailty using the Hospital Episode Statistics database [10]. Second, the most prevalent variables were used to make the HFRS using International Classification of Diseases, 10th Revision Clinical Modification (ICD-10-CM) codes [10]. Finally, the HFRS was validated by investigating the adverse outcomes of 2 cohorts of emergency admissions from the UK's Hospital Episode Statistics (HES) database, and then compared to existing frailty scores [10].

For the first step, 22,139 patients aged 75 years or older were randomly sampled from 3 specific regions in the UK [10]. The regions selected were Leicester, Nottingham, and Southampton due to their variable population representing both rural and urban populations in the UK [10]. These patients were grouped together for a cluster analysis using three variables for the clustering matrix: ICD-10-CM codes, inpatient days and hospital costs [10]. Each group was compared using admission history, the Charlson Comorbidity Index (CCI) and 2-year mortality so common variables could be identified [10]. A set of variables identified as predictors of frailty and their associated ICD-10-CM codes were used to create a frail cohort [10]. These

codes were derived by *Gilbert et al.* through collaboration with primary care, public health, and geriatric physicians. A total of 4,907 patients were identified as frail [10].

For the second step, ICD-10-CM codes for variables that were twice as prevalent in the frail cohort were extracted to produce the HFRS [10]. Each variable was given an individual weighting in proportion to their ability predict membership of patient to a cluster which was based on logistic regression models [10]. This score was then tested using c-statistics. This yielded the final HFRS score, composed of 109 individually weighted variables and a total score **(Appendix 1)** [10].

For the third step, the score was validated using a local cohort of 569 patients and national UK cohort of 1,013,590. Patients scored from 0 to 99 when the HFRS was applied [10]. This was skewed to the right with the majority of patients having high scores [10]. The proportion of patients with 30-day mortality increased with increasing HFRS, until patients with a score of 15 and above, where mortality remained the same [10]. Therefore, the HFRS stratifies patients into 3 frailty risk groups: low risk (HFRS <5), intermediate risk (HFRS 5 to 15) and high risk (HFRS >15) [10]. The performance of the HFRS was further assessed using c-statistic, demonstrating a result of 0.60 [10]. This score performed as well as the CFS and the FI [10].

There are several strengths of this score. Firstly, the use of routinely collected healthcare data is independent of user-operator error from manual assessment of frailty [10]. Secondly, this score allows a time-efficient and broad risk stratification of frailty using many variables and is able be integrated into systems which use ICD-10-CM codes to automatically calculate scores [10]. Finally, this score can identity patients who don't commonly receive assessment for frailty, which is most older patients [10].

1.4. Chapter summary

This chapter outlines the two fundamental concepts to this thesis: CVD and frailty. Given advances to medical treatment for acute and chronic conditions and an ageing population, the prevalence of both CVD and frailty is increasing. CVD and frailty incur a significant burden to healthcare resources. The relationship between CVD and frailty is bidirectional. The next chapter describes the systematic review and narrative synthesis undertaken to summarise the evidence of the impact of the HFRS on the outcomes of patients with CVD. The remaining chapters in this thesis address the general research questions in this thesis which are:

1) What is the prevalence of frailty in patients admitted with acute CVD?
2) What are the clinical characteristics of frail patients admitted with acute CVD?
3) What are the specific causes of acute CVD admissions in frail patients?
4) What are the outcomes following acute CVD admissions in frail patients?

2. Chapter 2: Systematic review of the Hospital Frailty Risk Score in cardiovascular disease patients

2.1 Chapter overview

The HFRS is a relatively new tool to stratify frailty risk in patients. To date, there have been no studies to summarise the evidence about the use of the HFRS in CVD patients. This chapter summarises a systematic review of the prognostic impact of the HFRS in patients with CVD.

2.2 Systematic reviews

A systematic review is a form of secondary research study, defined as studies reviewing already published literature to provide an overall summary [87]. This contrasts with primary research studies which aim to answer a specific research question using the non-published data, often providing novel findings [87]. The primary aim of a systematic review is to identify all relevant literature on a given topic. This is performed via a thorough search, termed a search protocol [87]. Systematic reviews can be sub-classified into either narrative review, which are descriptive or meta-analyses, which aim to pool all studies and assess the overall outcome with minimal bias [87]. This decision is determined by the number, quality, and results of the articles extraction from the final screening against the inclusion criteria [87]. Given its rigorous process, systematic reviews provide high-quality evidence to analyse the current literature on the topic of CVD and frailty [87]. Furthermore, as all information about the given topic is pooled into one, thorough, succinct document, areas of further research can be accurately identified [87].

There are several strengths of systematic reviews. Firstly, bias can be reduced in systematic reviews due to their robust and explicit methodology, making the results reproducible for validation [87]. Secondly, as all studies are about the topic of interest, each included study can vary in population, outcome measurements, definitions of disease and confounders [87]. Therefore, systematic reviews are often more generalisable [87]. Thirdly, as mentioned, systematic reviews allow potential areas of future research to be identified. Finally, as all research on the topic is collated into one article, this makes finding answers to specific research questions easier and more accessible [87].

Systematic reviews have several limitations. Firstly, searches do not account for publication bias, defined as the selective publication of studies that have a positive result [87]. Secondly, the quality of a systematic review is dependent on the quality of the original studies included [87]. Thirdly, systematic reviews can be over-generalisable, rendering their translation to clinical practice by healthcare professionals ineffective [87]. Finally, for meta-analyses, high heterogeneity in study design and quality can result in inaccurate estimates, away from the true relationship [87].

2.3 Introduction

As mentioned throughout this chapter. There are a variety of tools to stratify frailty in the primary care and hospital setting [9-11, 86, 88]. The HFRS provides a means of quantifying frailty using a cumulative deficit model using 109 individually weighted ICD-10 codes [10]. The HFRS has been validated in a variety of countries, however, it is not yet widely used due to its reliance on ICD-10 codes [10, 89-91]. The HFRS has been shown to perform as well as other frailty measures and comorbidity measures when predicting adverse outcomes such as length of stay and all-cause mortality [92-95]. Therefore, the aims of this systematic review were to identify peer-reviewed articles investigating the prognostic use of the HFRS in patients

with CVD, to describe the prevalence, clinical characteristics and prognostic value of frailty in CVD patients, and finally to identify areas of further research on the topic of frailty and CVD. The findings from this study have been submitted for publication **(Appendix 2)**.

2.4 Methods

2.4.1 Search strategy and study selection

This systematic review was performed and reported in accordance with the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guidance [96]. The protocol for the systematic review was pre-registered with the *International Prospective Register of Systematic Reviews* (PROSPERO, CRD42022371883). A thorough search strategy was developed to identify relevant peer-reviewed articles. The search included 2 main key words and their synonyms ("cardiovascular disease" and "hospital frailty risk score"). This search strategy was used with 6 databases: MEDLINE via EBSCO, EMBASE via Ovid, AMED via EBSCO, AMED via EBSCO, CINAHLPlus via EBSCO, AgeLine via EBSCO and Web of Science (WOS). Specific terms were used for databases indexed with Medical Subject Heading (MeSH) terms. One reviewer (Balamrit Singh Sokhal) performed the search.

2.4.2 Inclusion and exclusion criteria

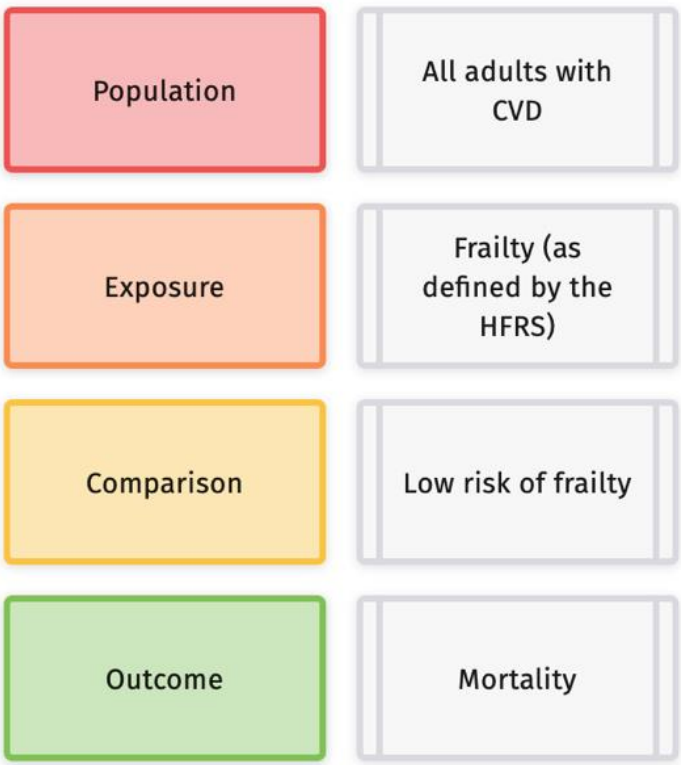
The population, exposure, control, and outcomes framework were used to develop the research question and design the inclusion criteria **(Figure** 2.1**).** The population was defined as all adults with CVD. The exposure was frailty as defined by the HFRS. The comparison was patients with low risk of frailty as defined by the HFRS. The primary outcome was mortality. The secondary outcomes were to describe prevalence of frailty and the clinical characteristics of frail patients. Observational studies conducted in the community, primary, or secondary care

were included. Qualitative studies, case reports, letters to the editor, conference abstracts and studies that measured frailty with other tools were excluded. There was no exclusion for language or age of the publication **(Table** 2.1**)**.

Table 2.1 Inclusion and exclusion criteria.

Inclusion criteria	**Exclusion criteria**
Studies investigating cardiovascular disease	Qualitative only studies (I.e., not mixed methods)
Studies using the Hospital Frailty Risk Score	Studies not investigating cardiovascular disease or frailty
Observational studies	Studies not using the Hospital Frailty Risk Score
	Systematic reviews
	Non-systematic reviews
	Conference abstracts
	Letters to the editor
	Cannot obtain abstract or full text

Figure 2.1 The systematic review research question in the form of the population, exposure, control, and outcomes framework.



2.4.3 Screening and data extraction

One reviewer (Balamrit Singh Sokhal) imported all references and removed exact duplicates. The remaining references were imported into Rayyan. One reviewer (Balamrit Singh Sokhal) screened all titles and removed references that did not meet the inclusion criteria. Two reviewers (Balamrit Singh Sokhal and Sowmya Prasanna Kumar Menon) screened abstracts and full texts independently to ensure no studies were incorrectly excluded. Any disagreements between reviewers were resolved by a third reviewer (Charles Willes).

Two reviewers (Balamrit Singh Sokhal and Sowmya Prasanna Kumar Menon) independently extracted data from full-text articles into pre-formed tables in Microsoft Word. Tables for data extraction included: first author, study year and country, study design, number and age of the participants stratified by frailty status, the prevalence and clinical characteristics of the participants stratified by frailty status, and all-cause mortality stratified by frailty status.

2.4.4 Quality assessment

Articles included were critically appraised by two reviewers (Balamrit Singh Sokhal and Sowmya Prasanna Kumar Menon) using the *Newcastle-Ottawa Quality Assessment for Cohort Study* tool [97]. Any disagreements were resolved by a third reviewer (Charles Willes). These validated tools function to assess the confounders, power, reproducibility, level of bias in the exposure and outcome variable and internal and external validity. Three domains are assessed: selection, comparability, and outcome. Each domain is comprised of multiple-choice outcomes and a ‘star’ to represent sufficient quality. The domain for selection assesses the representativeness of the cohort, cohort selection method, ascertainment of exposure and whether the exposure was present at the start of the study. The domain for comparability

assesses the quality of adjustment for confounders. The domain for outcome assesses how the outcome was identified, the length of follow-up, and adequacy of follow-up.[98].

2.4.5 Data synthesis and analysis

Given the heterogeneity between each study, a meta-analysis was not conducted. The extracted data was compared descriptively. The narrative synthesis was developed in accordance with the *Synthesis Without Meta-analysis* (SWiM) guidelines and the *Cochrane Handbook* [99, 100]. The SWiM guideline is a 9-item reporting checklist that provides a standardised approach to reporting systematic reviews in the absence of a meta-analysis.

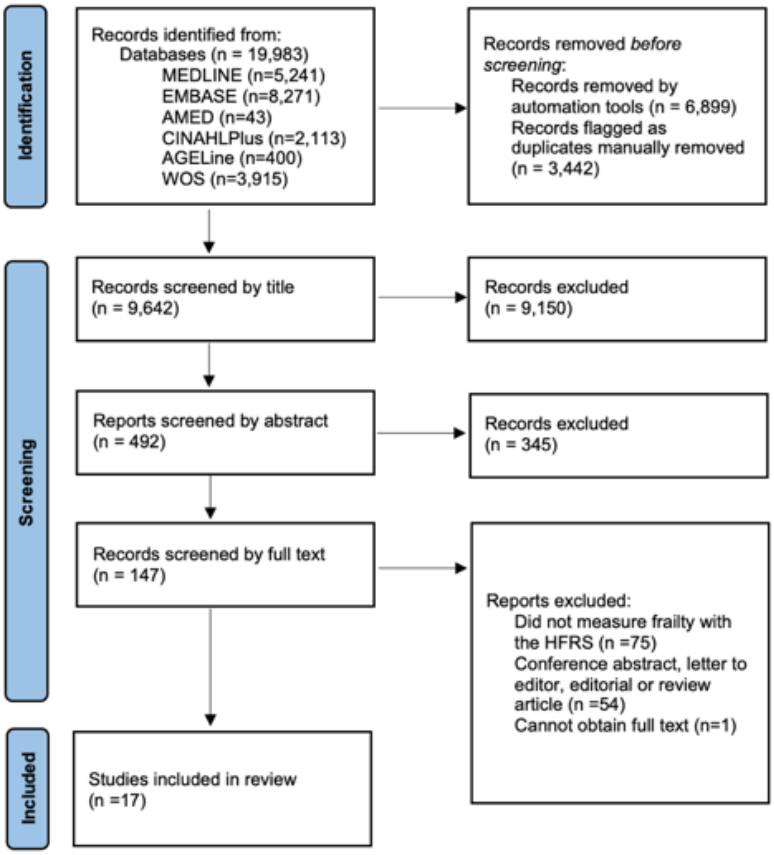
2.5 Results

2.5.1 Study characteristics

Following the search, MEDLINE via EBSCO yielded 5,241 results**.** EMBASE via EBSCO yielded 8,271 articles, AMED via EBSCO yielded 43 articles, CINAHLPlus via EBSCO yielded 2,113 articles, AgeLine via EBSCO yielded 400 articles and Web of Science yielded 3,915 articles for a total of 19,983 results (**Appendix 3-8)**. After exclusion of duplicates (10,341) and title (9,150) and abstract screening (345), 147 full texts were screened, and 17 studies included in the final analysis and underwent quality appraisal. Excluded studies during abstract screening included reviews, letters, editorials, conference abstracts (54), studies not using the HFRS (75), and full texts that could not be obtained (1) **(**

Figure 2.2**)**.

Figure 2.2 PRISMA flow chart of included results.



Abbreviations: CVD - Cardiovascular Disease; HFRS – Hospital Frailty Risk Score; WOS - Web of Science.

Of the 17 studies, all were retrospective cohort studies with 2 using propensity-score matching. Studies were conducted in Australia (N=9), US (N=4), Germany (N=2), Canada (N=1) and Korea (N=1). Across the 17 included studies, there was a total of 20,419,197 cases of CVD. Studies investigated HF (N=7), AMI (N=4), stroke (N=4), AF (N=1), cardiac arrest (N=1), and general CVD (N=1) which included primary hypertension, HF, AF, hypotension and chronic ischaemic heart disease.

There was varied reporting of each HFRS category. All studies described the prevalence of each HFRS category (N=17), whilst most studies described HFRS categories by age (N=10), clinical characteristics (N=10) and adjusted odds ratio (aOR) of mortality (N=13). Some studies classified a HFRS ≥ 5 as frail, hence combining the intermediate and high frailty groups (N= 6) and one study had a no risk (HFRS=0) category (N=1). All 17 studies were rated good quality according to the Newcastle-Ottawa Quality Assessment for Cohort Study tools **(Figure** 2.3**)**. From the 17 studies included using the HFRS, there were 20,419,197 cases of CVD. Studies were conducted in Australia (N=8), US (N=4), Germany (N=2), Canada (N=1) and Korea (N=1) **(Table** 2.2**)**. The median age of the low HFRS group ranged from 62.2 years to 83.6 years, the intermediate group ranged from 70.5 years to 84.3 years and the high HFRS group ranged from 75.1 years to 84.6 years **(Table** 2.3**)**.

Figure 2.3 Study quality assessment using Newcastle-Ottawa Quality Assessment Forms for Cohort Studies

Study	Representative -ness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis controlled for confounders	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Quality score
Kundi 2019	☆	☆	☆	×	☆	☆	☆	☆	Good
Kwok 2019	☆	☆	☆	×	☆	☆	☆	☆	Good
Smith 2019	☆	☆	☆	×	☆	☆	☆	☆	Good
Kwok 2020	☆	☆	☆	×	☆	☆	☆	☆	Good
McAllister 2020	☆	☆	☆	×	☆	☆	☆	☆	Good
Yang 2020	☆	☆	☆	×	☆	☆	☆	☆	Good
Zhang 2020	☆	☆	☆	×	☆	☆	☆	☆	Good
Kilkenny 2021	☆	☆	☆	×	☆	☆	☆	☆	Good
Lopez 2021	☆	☆	☆	×	☆	☆	☆	☆	Good
Nghiem 2021	☆	☆	☆	×	☆	☆	☆	☆	Good
Pinho 2021	☆	☆	☆	×	☆	☆	☆	☆	Good
Schnieder 2021	☆	☆	☆	×	☆	☆	☆	☆	Good
Sharma 2021	☆	☆	☆	×	☆	☆	☆	☆	Good
Borovac 2022	☆	☆	☆	×	☆	☆	☆	☆	Good
Sharma 2022	☆	☆	☆	×	☆	☆	☆	☆	Good
Sharma 2022	☆	☆	☆	×	☆	☆	☆	☆	Good
Sharma 2022	☆	☆	☆	×	☆	☆	☆	☆	Good

Table 2.2 Selected study characteristics.

Study	Study design	Country	Study period	Sample size	Participant inclusion criteria
General CVD cohort					
Nghiem 2021[a]	Retrospective cohort	Australia	2012-2015	115,946	Over 75 with CVD (primary hypertension, HF, AF, hypotension,

					chronic ischaemic heart disease)
HF cohort					
Kwok 2020	Retrospective cohort	United States	2004-2014	11,626,400	Adult (>18) hospitalisations for HF
McAllister 2020	Retrospective cohort	Canada	2004-2016	26,626	First time adult (>18) hospitalisation for HF
Sharma 2021[a]	Retrospective cohort;	Australia	2015-2019	3,706	First time adult (>18) hospitalisation for HF
Sharma 2022	Retrospective cohort	Australia	2013-2020	5,735	Older than 75 with HF
Sharma 2022[a,b]	Retrospective propensity-matched cohort	Australia	2013-2020	5,734	Adults (>18) hospitalised with HF
Sharma 2022[a,c]	Retrospective propensity-matched cohort	Australia	2013-2019	4,913	Adults (>18) hospitalised with HF
AMI and HF cohorts					
Kundi 2019	Retrospective cohort	United States	2016	785,127	Medicare fee-for-service beneficiaries 65 years and older admitted with AMI, HF or pneumonia
AMI cohorts					
Kwok 2019	Retrospective cohort	United States	2004-2014	7,393,268	Adult (>18) hospitalisations for ACS
Lopez 2021	Retrospective cohort	United States	2003-2008	2,761	Over 80 hospitalised with AMI
Borovac 2022	Retrospective cohort	United States	2015-2017	429,070	Adults (>18) hospitalised with STEMI
Stroke cohorts					
Zhang 2020	Retrospective cohort	Australia	2009-2013	15,482	Adults (>18) with intracerebral haemorrhage
Kilkenny 2021[d]	Retrospective cohort	Australia	2009-2013	15,468	Adults (>18) with stroke and TIA
Pinho 2021[e]	Retrospective cohort	Germany	2012-2017	489	Hospitalisations for acute ischemic stroke receiving endovascular treatment
Schnieder 2021[a]	Retrospective cohort	Germany	2015-2019	318	Hospitalisations for acute ischemic stroke receiving endovascular treatment for large vessel occlusion stroke

Cardiac arrest cohort					
Smith 2019[a]	Retrospective cohort	Australia	2008-2017	388	All in-hospital cardiac arrest involving rapid response team attendance
AF cohort					
Yang 2020[f]	Retrospective cohort	Korea	2005-2015	262,987	Adults (>18) with non-valvular AF

[a] Study defined frailty as a HFRS ≥ 5.
[b] Cohorts separated into 4 groups: frail and non-frail with and without specific pharmacotherapy
[c] Study investigated whether admission under general medicine or cardiology specifically impacted outcomes.
[d] Study included a no risk frailty group (HFRS=0).
[e] Study divided outcomes into favourable and poor at 3-months.
[f] Study investigated different clinical management pathways (ABC and no ABC) and effect of HFRS specifically.
Abbreviations: aOR – Adjusted odds ratio; AF – Atrial Fibrillation; AMI – Acute Myocardial Infarction; CVD – Cardiovascular Disease; CI – Confidence Interval; HF – Heart Failure; HFRS – Hospital Frailty Risk Score; NSTEMI – Non ST-Elevation Myocardial Infarction; STEMI – ST-Elevation Myocardial Infarction; TIA – Transient Ischaemic Attack.

Table 2.3 Selected study results.

Study	HFRS Category	Prevalence by HFRS category, %	Age in years	Clinical characteristics of high HFRS category, %	Odds of mortality with low HFRS reference group, aOR [CI)]
General CVD cohort					
Nghiem 2021[a]	Low	24.6	82.4 ± 5.2	High HFRS group were more likely to be female (54.6), have a Charlson score above 2 (86.8), have a length of stay beyond 10 days (32.9).	Bivariate analysis of 30-day mortality with high relation coefficient (0.92, p<0.01) Intermediate/High: 1.73 for all CVD, 2.15 for primary hypertension, 2.31 for HF, 2.52 for AF, 2.65 for hypotension and 2.56 for chronic ischaemic heart disease.
	Intermediate	34.5	83.7 ± 5.5		
	High	40.9	84.1 ± 5.5		
HF cohort					
Kwok 2020	Low	80.0	72.0 ± 15.0	Greater proportion of female patients in intermediate (53.4) and high (55.9) groups. Greater prevalence of previous stroke (17.2) and peripheral vascular disease (15.4), for high frailty risk group.	Intermediate: 1.52 [1.50-1.54] High: 1.60 [1.35-1.90] All p<0.001
	Intermediate	19.9	76.0 ± 13.0		
	High	0.1	81.0 ± 11.0		
McAllister 2020	Low	66.6	75.7 ± 13.0	Higher HFRS group were more likely to have	Results not presented as odds ratios. 30-day
	Intermediate	26.4	80.5 ± 11.6		
	High	6.9	82.7 ± 10.3		

				higher Charlson, female sex and decreased likelihood of baseline independence, more prior emergency department visits and more prior hospitalizations.	mortality presented as crude rates.
Sharma 2021[a]	Low	76.4	75.2 ±1 4.4	High HFRS group were more likely to be female (67.8), have a higher Charlson score (3.9).	30-day all-cause mortality: Intermediate/High: 4.12, [2.71–6.27], p < 0.001
	Intermediate	22.0	79.4 ± 12.3		
	High	1.6	82.5 ± 11.1		
Sharma 2022	Low	86.1	75.4 ± 14.3	High HFRS group were less likely to be female (40.6) and more likely to have a higher mean Charlson score (3.0) and increased length of stay (8.7).	30-day all-cause mortality: Intermediate: 1.52 [1.20-1.93] High: 2.09 [1.21-3.60]
	Intermediate	12.4	79.9 ± 11.3		
	High	1.6	82.4 ± 1.6		
Sharma 2022[a,b]	Low	7.5.5	Characteristics for each frailty category not described.	Characteristics for each frailty category not described.	In-hospital all-cause mortality of frail patients receiving pharmacotherapy: Intermediate/High: 0.20 [0.15-0.27]
	Intermediate/High	24.5			
Sharma 2022[a,c]	Low	76.2	Characteristics for each frailty category not described.	Characteristics for each frailty category not described.	Outcomes for each frailty category not compared to lower frailty category.
	Intermediate/High	23.8			
AMI and HF cohorts					
Kundi 2019	Low	49.3 for AMI, 27.5 for HF	Characteristics for each frailty category not described. Mean age of AMI cohort was 77.4±8.7, and HF cohort was 80.1±9.0	Greater proportion of female patients in intermediate (48.5%) and high (47.5%) group. Those with higher HF RS had greater prevalence of HF (4.5%), AF (30.5%), previous stroke (19.3%), peripheral vascular disorders (15.7%), chronic lung disease (20.6%), renal failure (50.9%), liver failure (1.9%), and dementia (60.3%).	30-day in-hospital all-cause mortality: Intermediate: 3.73 [3.66-3.80] High: 2.57 [2.18-3.04] All p<0.001.
	Intermediate	36.8 for AMI, 47.4 for HF			
	High	13.9 for AMI, 25.0 for HF			

			AMI cohorts		
Kwok 2019	Low	86.5	66±14	Greater proportion of female patients in intermediate (48.5%) and high (47.5%) group. Those with higher HF RS had greater prevalence of HF (4.5%), AF (30.5%), previous stroke (19.3%), peripheral vascular disorders (15.7%), chronic lung disease (20.6%), renal failure (50.9%), liver failure (1.9%), and dementia (60.3%).	30-day in-hospital all-cause mortality: Intermediate: 3.73 [3.66-3.80] High: 2.57 [2.18-3.04] All p<0.001
	Intermediate	13.4	75±13		
	High	0.1	80±11		
Lopez 2021	Low	59.1	83.6 ± 2.7	High HFRS group were more likely to be female (59.8), and have history of HF (38.7), cerebrovascular disease (40.9), dementia (35.1), chronic pulmonary disease (23.8), renal disease (23.5), cancer (23.2) and higher Charlson score (3.9).	30-day all-cause mortality with HFRS in model: Intermediate: 1.40 [1.10-1.79] High: 1.58 [1.12-2.24]
	Intermediate	29.0	84.3 ± 2.8		
	High	11.9	84.6 ± 2.7		
Borovac 2022	Low	71.6	62.2 ± 12.9	High HFRS group were more likely to be female (48.9), less likely to be white (69.5), smoke (0.8) and receive PCI (22.6). High HFRS group had lower prevalence of arterial hypertension (29.8) and dyslipidaemia (43.3). High HFRS had a higher prevalence of peripheral	Intermediate: 4.02 [3.91-4.13] High: 4.63 [4.36-4.92]
	Intermediate	26.3	70.5 ± 13.7		
	High	2.1	75.1 ± 12.7		

				artery disease (10.6), AF (27.4), anaemia (40.5) and renal failure (44.9).	
Stroke cohorts					
Zhang 2020	Low	25.0	Characteristics for each frailty category not described.	Characteristics for each frailty category not described.	Univariate model hazard of death after intracerebral haemorrhage: Intermediate: 1.18 [0.96-1.44] p=0.115 High: 1.70 [1.37-2.10] p<0.001 Multivariate model: Intermediate: 1.78 [1.33-2.39] p<0.001 High: 1.34 [1.03-1.75] p=0.032
	Intermediate	48.0			
	High	27.0			
Kilkenny 2021[d]	No risk (HFRS=0)/ Low risk (HFRS=1-4)	9.0 for no risk, 23.0 for low risk	67.0 (57.4-75.6) for no risk (HFRS=0), 71.5 (60.8-80.5)	High HFRS group were more likely to be female (55.5), suffer severe stroke (16.5) and have more comorbidities, history of stroke and length of stay.	30-day all-cause mortality compared to no-risk group Low: 0.95 [0.70-1.28] Intermediate: 2.08 [1.62-2.67] High: 3.55 [2.80-4.52] 90-day all-cause mortality compared to no-risk group Low: 1.06 [0.82-1.36] Intermediate: 2.29 [1.85-2.84] High: 4.33 [3.41-5.49]
	Intermediate	45.0	76.1 (65.4-83.8)		
	High	22.0	82.2 (74.3-87.5)		
Pinho 2021[e]	Low	2.0	Characteristics for each frailty category not described.	Characteristics for each frailty category not described.	'Favourable' 3-month outcome defined by modified Rankin scale of 0-2. High: 0.48 [0.26-0.89] (p=0.020)
	Intermediate	68.3			
	High	29.7			
Schnieder 2021[a]	Low	75.1	78.9 (9.6)	High HFRS group were more likely to be female (71.4).	90-day all-cause mortality: High: 1.12 [1.02-1.24] p=0.020
	Intermediate	22.7	83.8 (9.6)		
	High	2.2	84.2 (7.2)		
Cardiac arrest cohort					
Smith 2019[a]	Low	81.4	Characteristics for each frailty category not described.	Characteristics for each frailty category not described.	In-hospital mortality: Intermediate/High: 2.80 [1.52-5.15] p<0.001
	Intermediate/High	18.6			
AF cohort					
Yang 2020[f]	Low	84.2	Characteristics for each frailty category not described.	Characteristics for each frailty category not described.	Outcomes for each frailty category not described.
	Intermediate	14.2			
	High	1.6			

[a] Reported as per study as median with IQR, or mean with SD.
[b] Study defined frailty as a HFRS ≥ 5.
[c] Cohorts separated into 4 groups: frail and non-frail with and without specific pharmacotherapy
[d] Study investigated whether admission under general medicine or cardiology specifically impacted outcomes.
[e] Study included a no risk frailty group (HFRS=0).
[f] Study divided outcomes into favourable and poor at 3-months.
[g] Study investigated different clinical management pathways (ABC and no ABC) and effect of HFRS specifically.
Abbreviations: aOR – Adjusted odds ratio; AF – Atrial Fibrillation; AMI – Acute Myocardial Infarction; CVD – Cardiovascular Disease; CI – Confidence Interval; HF – Heart Failure; HFRS – Hospital Frailty Risk Score; NSTEMI – Non ST-Elevation Myocardial Infarction; STEMI – ST-Elevation Myocardial Infarction; TIA – Transient Ischaemic Attack.

2.5.2 Prevalence and clinical characteristics of frail patients

The prevalence of low frailty risk ranged from 2.0% to 86.5%, compared to 12.4% to 68.3% for intermediate frailty risk and 1.6% to 40.9% for the high frailty risk group. The average age of the low HFRS group ranged from 62.2 years to 83.6 years, compared 70.5 years to 84.3 years for the intermediate HFRS group and 75.1 years to 84.6 years for the high HFRS group. Increasing frailty score was generally associated with female sex and an increased prevalence of comorbidities, increased length of stay and increased odds of all-cause mortality **(Table** 2.3**)**.

2.5.3 The hospital frailty risk score and general cardiovascular disease

One study from *Nghiem et al.* investigated the impact of the HFRS in general CVD patients aged over 75 years [101]. The prevalence of low frailty risk was 24.6%, intermediate frailty risk was 34.5% and high frailty risk was 40.9%. The average age of the high frailty risk group was 84.1 years, compared to 83.7 years for the intermediate frailty group and 82.4 years for the low frailty risk group. The high HFRS group were more likely to be female (54.6%), have a Charlson Comorbidity Index (CCI) above 2 (86.8%), and increased length of stay beyond 10 days (23.9%). This study reported specific diagnoses of AF, HF, primary hypertension, hypotension and chronic ischaemic heart disease. The age, prevalence and clinical characteristic for patient cohorts with each diagnosis was not described. This study combined the intermediate and high frailty risk group to report 30-day mortality in comparison to the low

risk group. Bivariate analysis had a significantly high relation coefficient (0.92, $p<0.01$) and was reported over logistic regression as the regression results were determined to be biased. For the combined intermediate/high frailty risk group, odds of mortality using bivariate analysis was 1.73 for general CVD compared to the low frailty risk group. When stratified by diagnosis, odds of 30-day all-cause mortality using bivariate analysis was 2.15 for primary hypertension, 2.31 for HF, 2.52 for AF, 2.65 for hypotension and 2.56 for chronic ischaemic heart disease compared to the low frailty risk group. There were no confidence intervals reported in this study **(Table** 2.3**)**.

2.5.4 The hospital frailty risk score and heart failure

Eight studies utilised the HFRS in a HF cohort [90, 91, 101-106]. The prevalence of low frailty risk ranged from 24.6% to 86.1%, intermediate frailty risk ranged from 12.4% to 47.4%, and high frailty risk ranged from 0.1% to 13.9%. The average age of HF patients at low risk ranged from 72.0 years to 82.4 years, intermediate risk ranged from 76.0 years to 80.5 years, and high frailty risk ranged from 81.0 years to 82.7 years. Increasing HFRS category was mostly associated with an increased likelihood of female sex – with 1 study observing decreasing prevalence - a higher prevalence of cardiovascular and non-cardiovascular comorbidities and CCI, and increased length of stay. The aOR of 30-day all-cause mortality ranged from 1.52 (95%CI [1.50-1.54]) to 2.80 (95%CI [2.70-2.90]) in patients at intermediate risk, and 1.60 (95%CI [1.35-1.90]) to 3.50 (95%CI ([3.40-3.68]) for patients at high risk, compared to their low-risk counterparts **(Table** 2.3**)**.

2.5.5 The hospital frailty risk score and acute myocardial infarction

Four studies utilised the HFRS in an AMI cohort [89, 102, 107, 108]. The prevalence of low frailty risk ranged from 49.3% to 86.5%, intermediate frailty risk ranged from 13.4% to 36.8%,

and high frailty risk ranged from 0.1% to 13.9%. The age of AMI patients at low risk ranged from 62.2 years to 83.6 years, at intermediate risk ranged from 70.5 years to 84.3 years, and high frailty risk ranged from 80.0 years to 84.6 years. Increasing HFRS category was associated with increased likelihood of female sex, lower likelihood of being white, and a higher prevalence of cardiovascular and non-cardiovascular comorbidities and CCI. The aOR of mortality ranged from 1.40 (95%CI [1.10-1.79]) to 4.02 (95%CI [3.91-4.13]) in patients at intermediate risk, and 1.58 (95%CI [1.12-2.24]) to 4.63 (95%CI [4.36-4.92]) for patients at high risk, compared to their low-risk counterparts **(Table** 2.3**)**.

2.5.6 The hospital frailty risk score and stroke

Four studies used the HFRS in the overall stroke cohort (stroke, TIA or intracerebral haemorrhage) [95, 109-111]. Not all studies reported every outcome. The prevalence of intermediate frailty risk ranged from 45.0% to 48.0%, and high frailty risk ranged from 22.0% to 27.0%. The age of stroke patients at intermediate risk ranged from 76.0 years to 83.8 years, and high frailty risk ranged from 81.0 years to 84.2 years. Increasing HFRS category was associated with an increased likelihood of female sex, increased prevalence of comorbidities and increased length of stay. Of the 2 studies that reported aOR of 30-day mortality, this ranged from 1.78 (95%CI [1.33-2.39]) to 2.08 (95%CI [1.62-2.67]) in patients at intermediate risk, and 1.34 (95%CI [1.03-1.75]) to 3.55 (95%CI [2.80-4.52]) for patients at high risk, in comparison to their low-risk counterparts **(Table** 2.3**)**.

2.5.7 The hospital frailty risk score and atrial fibrillation

Two studies used the HFRS in an AF cohort [101, 112]. Neither study described the age distribution or clinical characteristics in each HFRS category. One study reported non-valvular AF patients exclusively [113]. The prevalence of intermediate frailty risk in was 14.2% and

high frailty risk was 1.6% [113]. This study did not report outcomes stratified by frailty risk category. The study of general CVD reported an aOR of 30-day mortality of 2.52 for combined intermediate/high frailty risk patients compared to their low frailty risk counterparts [101]. There was no CI reported for this result **(Table** 2.3**)**.

2.5.8 The hospital frailty risk score and cardiac arrest

One study used the HFRS in a cardiac arrest cohort [114]. This study described frailty as HFRS ≥ 5, combining intermediate and high risk scores under this category. The prevalence of low frailty risk was 81.4% and intermediate or high frailty risk was 18.6%. This study did not describe the distribution of age, prevalence and clinical characteristics of each HFRS category. The odds of 30-day in-hospital mortality was 2.80 (95%CI [1.52-5.15]) for the intermediate/high frailty group, compared to the low-risk group **(Table** 2.3**)**.

2.6 Discussion

2.6.1 Main findings

This is the first systematic review of the utility of the HFRS to investigate the prevalence of frailty in CVD patients, clinical characteristics of frail patients with CVD, and likelihood of mortality of frail patients with CVD. Frailty is associated with an increased hospital length of stay, total costs, adverse health outcomes and mortality [4]. There is a paucity of data on the prognostic ability of the HFRS in CVD-specific cohort. There are several important findings from this review that adds to the current body of literature exploring the relationship between CVD and frailty. This review also identifies potential areas for further research. Firstly, intermediate and high frailty risk is present in a substantial proportion of patients across a range of CVD. Secondly, increasing HFRS is associated with increased age, female sex, non-white

race, and comorbidities. Thirdly, higher frailty incurs a greater healthcare burden, with increased HFRS associated with increased length of stay and total charges. Finally, the HFRS is significantly associated with increased mortality across most CVD.

The impact of frailty on outcomes varies with frailty measure, study setting and length of follow up [90]. Frailty has been shown to increase odds of CVD by 35% [22]. In turn, CVD increases the odds of frailty, demonstrating a bidirectional relationship [22]. The positive correlation is observed using most frailty measures including the HFRS which performs as well as most frailty and comorbidity tools as determined by area under receiver operating curves [10, 92, 94]. There are multiple underlying mechanisms linking CVD and frailty. In summary, both frailty and CVD are age-related conditions causing a pro-inflammatory state, with increased levels of pro-inflammatory cytokines and immune markers such as interleukin 6 and C-reactive protein [115]. Increased inflammation perpetuates a cycle of frailty, driving sarcopenia and leading to adverse health outcomes [80]. In the context of CVD, the presence of inflammation drives atherosclerosis and plaque instability, leading to increased likelihood of plaque rupture and associated complications [73]. Therefore, CVD and frailty drive one another and are major public health priorities [116].

2.6.2 Prevalence of frailty

There are many validated tools to assess frailty, yet there is no consensus on which tool to use [117]. As developed countries transition to digital systems, there is increasing reliance on electronic health care records and automation of processes to ensure efficiency and optimisation of patient care [118]. The HFRS was derived entirely from routinely collected health record data using ICD codes and then validated on a UK cohort [10]. The HFRS has since been used with Australian, United States, and German CVD cohorts [89, 91, 110]. The performance of the HFRS is comparable to other digital health record frailty measures and

other well-known measures such as the Frailty Index and Clinical Frailty Scale [10, 94]. However, most studies comparing tools do not investigate patients with CVD specifically.

The reported prevalence of frailty is highly variable in the literature as it is dependent on the frailty measure used [16]. A meta-analysis of 31,343 community-based participants estimated the prevalence of frailty to be around 17.9%, however, none of the included studies used the HFRS [16]. This systematic review suggests the prevalence of frailty as defined by the HFRS in CVD ranges between 12.4-48.0% for intermediate risk, and 0.1-40.9% for high risk. Such a range in prevalence could be due to the specific CVD of interest or the criteria of cohort selection. Reported prevalence values seemingly remained constant across studies investigating the same CVD. However, studies vary in participant inclusion criteria. Most frailty studies have a minimum age cut-off of 65 or 75 years; yet this review found some studies also included all adult hospitalisation with no age restrictions [101]. As frailty is related to ageing, studies adopting age restrictions would have a larger proportion of patients at risk of frailty, rendering them less generalisable to the entire population [4, 6, 16].

2.6.3 Frailty and clinical characteristics

This study found the increasing HFRS was mostly associated with female sex, non-white race, and increased prevalence of comorbidities. Most measures of frailty demonstrate increased prevalence of frailty in females, patients from non-white racial groups and patients with multimorbidity [5, 7, 78]. There are a variety of factors implicated in this relationship. Women are more likely to have a higher percentage body composition of fat and are more affected by biological and socio-economic factors of frailty [119, 120]. Non-white race may be a factor in the development of frailty, even after adjustment for age, sex and socio-economic status, however the mechanisms behind this are poorly understood, with conflicting results between studies [121, 122]. Many studies corroborate increasing frailty with increasing comorbidity

burden. Whilst both overlap, both have two distinct process, both related to age [123]. The normal physiological process of ageing, and it's interaction with diseases leads to the development of frailty [123]. Comorbidities play a distinct role in introducing the ageing patient to acute stressors, leading to rapid decline in functional abilities in a frail patient [123]. As the HFRS was formed as a cumulative deficit model of over 109 comorbidities ranging from dementia to infection, patients with increased HFRS are inherently more likely to also have more comorbidities [10].

2.6.4 Frailty and mortality

In this systematic review, increasing HFRS category was associated with increased odds of all-cause mortality across all CVD. This supports previous literature corroborating frailty, as defined by most other measures, associated with an increase in the odds of all-cause mortality from CVD [16, 22, 115, 116]. In the pilot study where non-CVD specific cohorts were used, receiver operating curves for the HFRS predicting 30-day mortality, long hospital stay, and 30-day readmission was 0.60, 0.68 and 0.56 respectively with the performance of the categorised HFRS fairly overlapping with the Frailty Phenotype and Frailty Index scales, and the continuous HFRS demonstrating moderate agreement with Rockwood's Frailty Index [10]. Studies using the HFRS in non-CVD specific cohorts also demonstrate an increased odds of mortality with increasing HFRS, with some studies comparing the HFRS to other frailty measures demonstrating comparable performance [124, 125].

2.6.5 Clinical implications

The clinical implications of this study may be substantial given the increasing age and frailty of the population, the increasing prevalence of CVD, and the drive to digital systems in certain areas of the world that facilitate electronic health record data [6, 17, 126]. The drive toward

such systems prompts the utility of automated systems to improve efficiency, increase accuracy and identify needs of at-risk individuals based on their past medical history and risk factors [100]. Frailty is a reversible condition and progression can be mediated by earlier identification, assessment, and intervention to improve prognosis in CVD, though the possible outcomes of intervention have not been explored [9, 30, 117]. However, medications used to treat cardiovascular conditions may be contra-indicated in the frail elderly on the basis of a risk-benefit assessment [127]. This review provides assurance that the HFRS is a validated and important tool that can be used to risk stratify CVD patients.

2.6.6 Strengths and limitations

This systematic review has several strengths. Firstly, there was a systematic approach to identifying research articles guided by PRISMA guidelines, ensuring optimal identification of potential articles and minimisation of bias. Each abstract and full text was screened by two reviewers, with conflicts resolved by a third, independent reviewer. Secondly, the search strategy was comprehensive through the inclusion of all synonyms for each search term, verified by experts in cardiology, epidemiology and systematic reviews. This allowed for inclusion of most papers on the topic of CVD and frailty, allowing authors to specifically screen for the studies that included the HFRS. Thirdly, all major databases were searched. MEDLINE, EMBASE and Web of Science (WOS) are among the largest repositories for peer-reviewed research. This reassures the search for articles was comprehensive.

This systematic review has several limitations. Firstly, there was a large degree of heterogeneity between the study focus, study design and reporting of studies. Most studies reported mortality in the intermediate and high HFRS groups separately, whereas others combined both groups. For adjusted analysis, most studies used a low HFRS category as the reference group, but some studies used a HFRS of 0 as the reference group. In addition, studies

used different covariates for the multivariable analyses. This makes it difficult to compare results and yield accurate estimates. Secondly, not all studies described the prevalence or clinical characteristics of each HFRS cohorts. This decreases the confidence of the conclusions drawn in this review and its generalisability. Thirdly, restricting inclusion of studies to the English language only could have implications for the results of this study. Different populations may have different prevalence of diseases and therefore different frailty risk profiles according to the HFRS. Finally, all studies in this review were from countries that have made the transition to electronic health record keeping and hold registries. Some of these countries, especially US based, may be privatised, hence socio-economic status could act as a barrier to healthcare and therefore studies could be underestimating the burden of frailty. This means the review cannot be generalised to healthcare systems that do not utilise the ICD coding system or digital systems in general.

2.7 Conclusions

This study reassures that HFRS can be utilised to stratify patients admitted with CVD, and exhibit association with adverse outcomes in this population. However, the reporting of clinical characteristics and outcomes of the studies included are inconsistent and, in some cases, the HFRS is not the main focus of CVD studies. Further studies that stratify CVD patients by their HFRS categories are warranted to determine its effects in different CVD patient groups.

2.8 Thesis aims

This systematic review demonstrates that the use the HFRS has been sparsely used on CVD cohorts, with most studies focusing on AMI and HF patients. Other tools such as the CFS and FP have been widely used in the literature. Given the rigorous nature of the HFRS and the use

of routinely coded data being inherent to its use, the HFRS remains an understudied tool in the CVD population despite its predictive abilities.

There are multiple aims of this thesis. Firstly, using national emergency department (ED) and hospital datasets, this thesis aims to describe the prevalence of low, intermediate and high HFRS in a cohort of patients with CVD. There has been only one previous study using the HFRS in a general CVD cohort. However this study investigated 5 CVD in depth (primary hypertension, HF, AH, hypotension and chronic IHD). Furthermore, this study described the odds of mortality in a combined intermediate and high HFRS group, and not separately. This thesis hypothesises that frailty represents a significant proportion of the population as reported in previous studies.

Secondly, this thesis aims to describe the clinical characteristics of low, intermediate and high HFRS patients with CVD. Numerous studies have demonstrated that increased frailty is associated with increased age, female sex, non-white race and prevalence of comorbidities. This trend is generally seen across most studies using the HFRS in general and specific cohorts. This thesis hypothesises that increasing HFRS will follow a similar trend reported in previous studies.

Thirdly, this thesis aims to describe the specific causes of CVD in the low, intermediate and high HFRS patients. As with the prevalence of frailty in CVD, there is only one study using the HFRS stratifying a general CVD cohort into specific diseases. This thesis hypothesises that, in a cohort with general CVD, increasing frailty will be associated with age-related CVD such as stroke and HF.

Fourthly and finally, this thesis aims to describe the association of the HFRS with mortality in patients with CVD. Studies report the HFRS is associated with an increased odds of all-cause mortality across most CVD. This thesis hypothesises a similar trend to that reported in previous

studies using the HFRS, with increasing HFRS associated with increased odds of mortality in CVD.

2.9 Chapter summary

This chapter summarised the current evidence of the use of the HFRS in CVD patients. Most studies investigating CVD and frailty are limited to community studies or focus on one specific diagnosis. Furthermore, very few studies utilise the HFRS specifically in a CVD setting and given the continued progression to EHR data use in clinical practice, the HFRS can be a powerful tool for the prognostication of frail patients. More studies need to be done to investigate its use in patients with CVD specifically.

Therefore the aim of this thesis is to describe the prevalence, characteristics and mortality of CVD patients based on their HFRS. The next chapter outlines the methods involved to investigate these aims, through the analysis of national databases from the United States: the Nationwide Emergency Department Sample and the National Inpatient Sample.

3. Chapter 3: Methods

3.1 Chapter overview

This thesis uses national datasets from the United States (US). This chapter summarises the general methods of this thesis. Firstly, this chapter provides a brief introduction to the structure of healthcare in the US and an overview of electronic health record (EHR) data. Secondly, this chapter provides an overview of the two national US databases used in this thesis: the *National Emergency Department Sample* (NEDS) for emergency encounters and the *National Inpatient Sample* (NIS) for hospital admissions. Finally, this chapter will define the main variables used in the studies and how the analyses will be conducted to yield the results presented in this thesis.

3.2 Healthcare in the United States

The US utilises a combined public and private approach to healthcare, whereby individuals obtain health insurance coverage from private companies or government-subsidised health insurance [128]. According to the US Census results for 2021, 66.0% of US citizens are insured privately, 35.7% publicly and 8.6% are uninsured, with some citizens insured under multiple initiatives **(Table** 3.1**)** [129]. Broadly, there are 3 types of private health insurance: employment-based, where an insurance plan is provided by the employer or trade union, direct-purchase, where an insurance plan is obtained directly from a company and Tricare, where insurance is provided by the Civilian Health and Medical Program of the Uniformed Services [129]. The 2010 Affordable Care Act aimed to provide more universal healthcare, defined by the World Health Organisation (WHO) as "ensuring access to health services of sufficient quality to be effective without exposing the user to financial hardship", by launching health

insurance marketplaces to include individuals across all ages, races and income levels [128, 130]. Public health insurance can also be divided into 3 types: Medicare and Medicaid which are explained below and the Civilian Health and Medical Program of the Department of Veterans Affairs [129].

Table 3.1 United States healthcare insurance plans.

Public	**Private**
Medicare	Employer-based
Medicaid	Direct purchase
Civilian Health and Medical Program of the Department of Veterans Affairs	Tricare

Public healthcare insurance programmes such as Medicare and Medicaid were incepted in 1965 as part of the Social Security Act [131]. 18.4% of US citizens were insured by Medicare and 18.9% by Medicaid [129]. Medicare provides basic healthcare to patients over 65, or under 65 with a disability and is funded with tax revenue [131]. There are several types of coverage: Part A which covers care in the inpatient setting; Part B which covers general outpatient care such as procedures and diagnostic tests; Part C which is a combination of Part A and B and is more often offered by private companies; and more recently Part D which was introduced to cover prescription medications [131]. However, Medicare follows a co-insurance model, where part of the cost of healthcare is still paid for by the individual [131]. Medicaid follows a similar model to Medicare, but is specifically available to low-income individuals with no age restrictions, rendering Medicaid the largest source of funding for medical services to the US lowest income individuals [132]. Individuals not eligible for Medicare or Medicaid either self-pay or are privately insured [133].

In order to monitor events during episodes of healthcare provision, all US hospitals routinely code the services provided in order to yield accurate billing information [134]. These codes are recorded on EHR databases [134].

3.3 Electronic health record data

EHR data is collected by healthcare service providers and is used across different countries for different purposes. EHR data is widely used in the US by healthcare service providers for billing purposes, clinical information and high quality research **(Table** 3.2**)** [134].

Table 3.2 Examples of electronic health record datasets.

Public	
United States	Nationwide Emergency Department Sample
	National Inpatient Sample
	National Readmissions Database
	Nationwide Kids Database
	Medical Information Mart for Intensive Care
	Centre for Disease Control and Prevention
United Kingdom	Clinical Practice Research Datalink
	Hospital Episode Statistics
	National Vascular Registry
	Sentinel Stroke National Audit Programme
	National Institute for Cardiovascular Research Outcomes Datasets

There are several strengths of using EHR in research, including the impact on clinical, organisational and societal outcomes [135]. EHR databases can collect important clinical information such as diagnoses, symptoms, biomarker levels, medications, management and complications, patient information such as demographics and insurance status, and hospital information such as length of stay, total costs, hospital bed size, teaching status, and geographical region [136]. This information is routinely collected for every admission to a hospital that uses EHR data, and therefore EHR can provide vital information for entire populations, allowing insights into public health, chronic and communicable diseases [137]. Information is either anonymised or pseudo-anonymised [136].

Most EHR studies focus on improving patient safety and assessing intervention effectiveness and efficiency [135]. EHR studies facilitate high-impact research vital for clinical practice [135]. In addition, EHR data have driven research fundamental to public health and

preventative medicine by means of comparing patients with certain risk factors against a control group [135]. Generally, hospitals that invest in information technology and are involved in research have a higher quality of care [138]. Studies using EHR can have multiple methodologies, most commonly they are observational studies or longitudinal cohort studies [139]. Studies using EHR are relatively less expensive compared to surveys and are less likely to incur reporting bias and attrition bias [136, 137, 139].

There are several limitations to research using EHR. Firstly, different databases may not contain sufficiently granular information, for instance some databases lack information, or have low accessibility to information, about diet, physical activity, disease duration and medications which is particularly important for studies investigating CVD [140]. Secondly, EHR are potentially a source of coding inaccuracies and missing data [140]. Resultant misclassification or non-random missing data can result in inaccurate estimations [140]. Thirdly, there is a difficulty in defining incident and prevalent disease, as all comorbidities of a patient may be recorded upon the initial episode of care, therefore the length of time between diagnosis and treatment and coding onto the database is not known [140]. Furthermore, patients may predominantly present with more severe conditions meaning that databases could underestimate important but less severe conditions [140]. Some databases may only record in-patient episodes, and therefore lack post-discharge and primary care data, where most patient care occurs [141]. Fourthly, some studies using databases that include information on pharmacotherapy may experience confounding by indication, where a medication may cause paradoxical results in a study [139, 140]. Finally, due to data anonymization, databases may be focused on hospitalisation-related data leading to potential capture of same patient with multiple encounters [139, 140]. The NIS and NEDS are two examples of EHR datasets that will be used in this study [142].

3.4 Study design

The studies were designed as a retrospective cohort studies. Retrospective studies investigate readily collected data and look back in time to investigate both exposures and outcomes [143]. Both studies utilise data from the NEDS and NIS. Due to large sample size within the used datasets, the studies from this thesis contain significant statistical power given a large number of cases for the variables of interest. However, no formal power calculation was performed beforehand.

There are strengths and limitations to the retrospective cohort study design. Major strengths of cohort studies firstly consist of them being relatively inexpensive, less time-consuming, and generally less resource intensive when compared to prospective cohort studies [143]. This is because data has already been collected [143]. Secondly, particularly in the case of this thesis, large datasets are easily accessible and allow powered analyses leading to detection of less prominent variations between studied groups [143]. However, this warrants critical appraisal of clinical significance for each finding [143]. Finally, as mentioned, multiple aspects of a disease can be measured simultaneously, such as incidence, exposures, and outcomes. This is particularly suitable for examining rare diseases [143].

However, with this design there are inherent disadvantages. Firstly, there is less control over the variables included in the study, as only the variables that have been collected can be used [143]. Secondly, retrospective studies are susceptible to a variety of bias such as selection and information bias, which would decrease the precision of results through deviation from the true value [143]. Finally, confounding variables commonly introduces confounding bias into cohort studies [143]. Therefore, variables must be carefully considered and data must be accurately and thoroughly collected to allow stratification of confounding variables and inclusion in statistical models [143].

3.5 Study databases

3.5.1 The Nationwide Emergency Department Sample

The NEDS was developed by the Healthcare Cost and Utilization Project (HCUP) sponsored by the Agency for Healthcare Research and Quality (AHRQ). Data collection for the NEDS has been released annually since 2006. The NEDS provides information on 28 million annual ED visits from 989 hospitals across 40 states in the US. This is an approximate 20% stratified sample of all US hospital-based ED encounters. When weighted, the NEDS is designed to be representative of approximately 143 million annual ED encounters across the US, like the estimated total ED encounters in the US [144]. The NEDS has been used for a variety of analyses using the retrospective observational study design ranging from prognostic studies to validation studies [145, 146].

The NEDS provides information on ED encounters, irrespective of the disposition and outcomes. Such information includes hospital demographics, patient demographics, treatment, comorbidities and outcomes **(Appendix 9)** [142]. Patient demographics include age and sex. Hospital demographics include bed size, region, teaching status and whether the hospital is rural or urban. Hospital outcomes include ED discharge status. All information for the NEDS since 2015 was captured using ICD-10-CM codes. The large sample size means the NEDS is suitable for observational studies for even uncommon diseases and procedures. Coders are specifically trained to analyse medical discharge summaries and assign the correct code for billing purposes.

3.5.2 The National Inpatient Sample

The NIS is the largest available database of US hospitalisations developed for the Healthcare Cost and Utilization Project (HCUP), sponsored by the Agency for Healthcare Research and Quality (AHRQ). The first rendition of the NIS became available in 1988 and since then the AHRQ has released the NIS annually. The NIS contains anonymised data on diagnoses and procedures from over 7 million hospitalisations annually from 20% of US community hospitals, excluding rehabilitation and long-term acute care hospitals. Unweighted, this represents a 20% sample of all US hospitalisations [142]. When weighted, the NIS represents 97% of US hospitalisations which is approximately 35 million yearly hospitalisations.

The database contains both clinical and non-clinical information [147]. Examples of clinical information includes patient demographics, comorbidities and in-patient procedures whilst examples of non-clinical information include total inpatient costs and length of hospital stay, bed size and teaching status **(Appendix 10)** [147]. Information available on the NIS is derived from discharge summaries. The NIS has the capacity to record one primary discharge diagnosis, and up to 29 secondary diagnoses, as well as up to 15 procedures [147]. As with the NEDS trained coders analyse medical discharge summaries and assign the correct code. The NIS is coded using International Classification of Diseases code renditions. From the 1st of October 2015, the NIS uses ICD-10-CM [147].

To produce the sample, each discharge from all participating hospital is ordered by hospital, admission month and diagnostic group (e.g. cardiovascular diseases) [147]. Following this, every 5th discharge is extracted, producing a 20% sample [147]. Samples are then weighted to represent the entire population. To calculate weight, the expected number of hospital admissions is divided by the number of sampled admissions within a stratum [147]. Strata are hospital characteristics such as teaching status, location, bed size and importantly, census

region [147]. The US is divided into 9 census regions of the US: New England, Mid-Atlantic, East North Central, West North Central, South Atlantic, East South Central, West South Central, Mountain and Pacific **(**Error! Not a valid bookmark self-reference.**)** [147]. All admitted patients will have the same weight applied to them to produce national estimates. Overall the weighted sample includes approximately 35 million hospitalisations **(Figure** 3.2**)** [147].

Figure 3.1 Census regions for the NIS, *from HCUP [142]*.

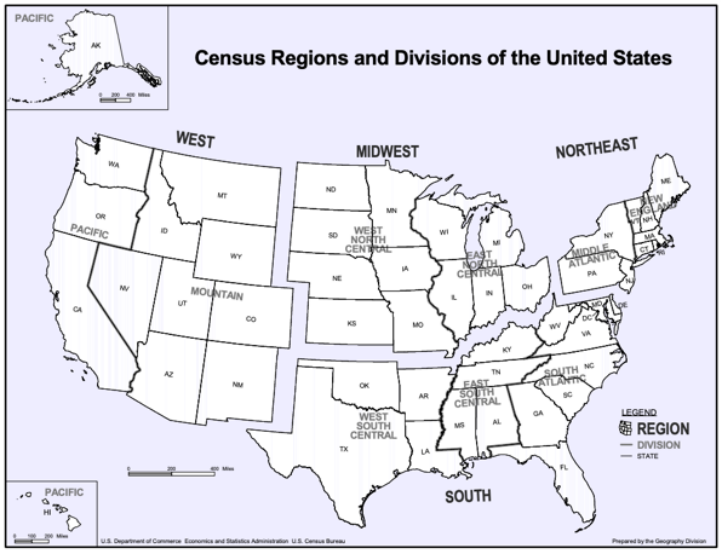
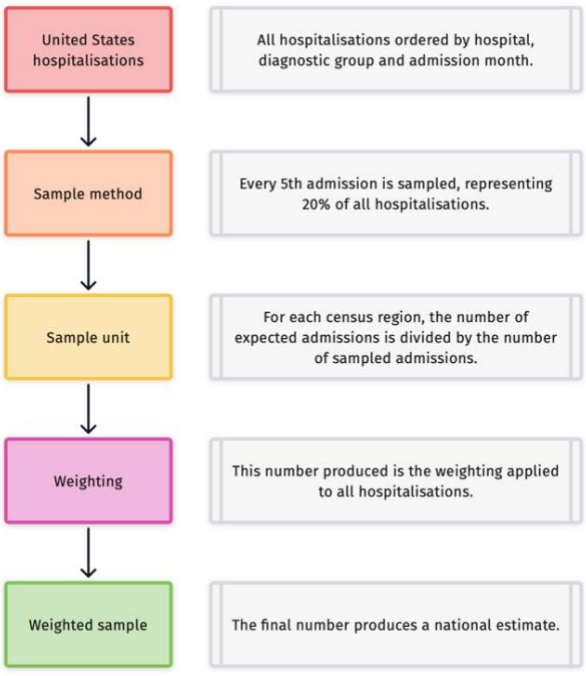


Figure 3.2 Flowchart of the sampling process.



3.5.3 Limitations

3.5.3.1 Internal validity

Limitations of the databases originate from their internal validity. Internal validity represents the ability of a study to accurately measure the intended outcomes, and therefore generate valid conclusions. The higher the internal validity of a study, the more confident investigators can be that the hypothesis is correct and not due to other variables unaccounted for. Internal validity is affected by random error, confounding and systematic errors such as selection and confounding bias.

3.5.3.2 Random error

Random error occurs due to chance and is more likely to happen with smaller datasets. Random error can be minimised by using large datasets as a larger sample size reduces type I and type II error [148]. The NEDS and NIS are national datasets containing data of millions of patients across the US. The large dataset means the chance of random error occurring is relatively small [148]. Furthermore, increased sample size and allows for even more precise estimates. Where 'acceptable' p-values are usually considered to be <0.05, it is common for studies using the NEDS and NIS to have p-values as small as <0.001. Therefore, significant results from these studies are less likely to be due to random error and chance [148].

3.5.3.3 Information and selection bias

Bias is defined as methods that introduce systematic errors during the conduction and analysis of a study, which favour one outcome that could deviate from the true outcome. Selection bias is defined as bias arising errors in how subjects are included in a study. This could lead to inaccurate conclusions for the same reasons as information bias. The systematic methods behind both information and selection bias are similar for the study datasets. The NIS and

NEDS are comprised of coded data primarily for billing purposes. Coded data could be subject to selection bias due to inaccurate coding or missing data [149]. Other types of selection bias that commonly occur in observational cohort studies do not apply in this study as coding is mandatory for all hospital encounters for billing purposes in the US [150]. This includes loss of follow up bias (participants previously engaged in the study, that are no longer able to be contacted), non-response bias (lack of information gained as participants are unable to respond), spectrum bias (due to a limited inclusion criteria) and survivor bias (where treatment effects are overestimated as those who have survived have received treatment for longer) among others [150]. Overall, coding for routinely collected healthcare data has been found to be relatively robust and acceptable for use in research [151]. However, the selection of codes for a particular condition could introduce inadvertent selection bias.

There is the potential for information and selection bias from the availability of, and the coding of data in the NIS and the NEDS. Information bias, also known as observational bias or misclassification bias, occurs as a form of measurement error, where there is inaccurate recall, recording or handling of the information of a study [149]. In this of both datasets, information bias contributes to selection bias.

3.5.3.4 Confounding

Confounding bias relates to the interference of individual's risk factors with the detection of direct association between the exposure of interest and outcome in the study. Therefore, the relationship between the exposure and outcome becomes unclear. Confounding bias is common in epidemiological studies however there are methods to minimise its effect through statistical adjustment [150]. There are different types of confounding bias: positive, negative, and unmeasured. Positive confounders are variables that overestimate the true effect of the exposure [150]. This leads to a smaller effect size in multivariate models. Negative confounders

cause the opposite as they are inversely associated with the outcome [150]. Therefore, negative confounding variables underestimate the true effect of the exposure such that when they are adjusted for, the effect size is larger [150]. Unmeasured confounding occurs when relevant confounders are not accounted for in the adjustment models [150]. Most confounders can be accounted for with careful selection of adjustment variables, as to minimise their effect and yield a value closer to the true value [150]. The NEDS and the NIS cover a broad range of diagnoses, procedures, and outcomes due to the use of the ICD-10-CM classification system, meaning that many potential confounders can be identified and accounted for [152]. However, factors highly relevant to CVD are not covered by either database, such as diet, exercise level, pharmacotherapy and biomarker levels [152]. This information could have implications on the outcomes of studies conducting uses the databases, in particular CVD studies, as a significant number of patients diagnosed with any form of CVD are medically treated. Therefore, conclusions from studies are prone to misestimations [152]. Finally, both databases only capture information on in-hospital events and therefore, more detailed analysis of longitudinal outcomes cannot be assessed.

3.6 International Classification of Diseases, Tenth Revision

The ICD-10 system is the official diagnosis and procedure classification for US hospitals and has been used by the NIS since 1st October 2015 (previously the 9th edition of the codes was used) [153]. The ICD system was created to monitor diseases and provide accurate tracking of medical procedures for hospital charges in the US [153]. The ICD system is also used internationally by over 100 countries to provide accurate mortality statistics [153, 154]. ICD-10 was developed to allow for greater richness of data in comparison to its predecessor, containing around 155,000 codes compared to the previous 17,000 [153]. The ICD-10 codes are split into 3 volumes: the 1st contains lists of cause-of-death titles and codes; the 2nd contains

inclusion and exclusion terms for cause-of-death titles; and the 3rd contains an index of diseases and natures of injury and external causes of injury. The ICD-10 codes consist of 3 to 7 characters, the first character is a letter which assigns the code to a chapter [153]. The second and third characters are numbers, and the remaining characters are a combination of letters and numbers [153]. The combination of the first 3 numbers is representative of common traits, with each number assigned toa specific trait. As mentioned, both the NEDS and the NIS use ICD-10-CM codes when billing patients. Therefore, ICD-10-CM codes can be used in research to extract specific study variables from the NEDS and NIS databases. Accurate coding is required to ensure valid analysis of data to draw conclusions.

3.7 Study variables

3.7.1 Independent

The independent variable is defined as a variable that will not be affected by another but can influence the dependent variable. For this thesis, the independent variable is the HFRS. As mentioned in Chapter 1 the HFRS is comprised of many variables sourced entirely from ICD-10-CM codes, allowing analysis with routinely collected EHR data that holds the variable included. The NEDS and the NIS are coded using ICD-10-CM, therefore, each individual clinical encounter in the ED or in-hospital, can be classified according to their HFRS into the 3 groups outlined in the original study: low risk (HFRS <5); intermediate risk (HFRS 5 to 15); and high risk (HFRS >15) [10]. Each variable was used and weighted according to the original study [10].

Other independent variables used were the 7 CVD admission of interest: AMI, AF, acute ischaemic stroke, HF, PE, cardiac arrest and acute haemorrhagic stroke. The parent code for AMI was I21.x. The parent code for AF was I48.x. The parent code for acute ischaemic stroke

was I63.x. The parent code for HF was I11, I13, I42 and I50.The parent code for PE was I26.x. The parent code for cardiac arrest was 146.x. The parent code for acute haemorrhagic stroke was 160.x, 161.x and 162.x **(Table** 3.3**)**.

Table 3.3 ICD-10 codes used in this thesis.

Variables	Source	Codes
Acute ischaemic stroke	ICD-10	I63
Acute haemorrhagic stroke	ICD-10	430, 431, 432.0, 432.1, 432.9
Heart Failure	ICD-10	I50, I42
AF	ICD-10	I48.91, I48.20-21, I48.11, I48.19, I4.80
Cardiac arrest	ICD-10	I46.2 (due to cardiac condition); I46.8 and I46.9 (due to non-cardiac condition)
Acute MI	ICD-10	410.0x, 410.1x, 410.2x, 410.3x, 410.4x, 410.5x, 410.6x, 410.7x, 410.8x, 410.9x
Pulmonary embolism	ICD-10	I26
Dyslipidaemia	ICD-10	E78
Smoker	ICD-10	Z72.0
Previous MI	ICD-10	I25.2, I25.6
Previous PCI	ICD-10	Z98.61, Z95.5
Previous CABG	ICD-10	Z95.1, Z95.5
Thrombocytopenia	ICD-10	D69.4, D69.5, D69.6
Homelessness	ICD-10	Z59.0
Chronic renal failure	ICD-10	N18
Hypertension	ICD-10	I10
Anaemias	ICD-10	D62, D63, D64
Diabetes Mellitus	ICD-10	E08, E09, E10, E11, E13
Coagulopathies	ICD-10	D65, D66, D67, D68, D69
Liver disease	ICD-10	K70, K72.1, K72.9, K73, K74, K75, K76, K77
Metastatic disease	ICD-10	C77, C78, C79, R18.0, C7B
PVD	ICD-10	I73
Valvular heart disease	ICD-10	I34, I35, I36, I37

Abbreviations: AF: atrial fibrillation; CABG – coronary artery bypass grafting; CVA: cerebrovascular accident; ICD-10 – International Classification of Diseases Tenth Edition Clinical Modification; MI – myocardial infarction; PCI: percutaneous coronary intervention; PVD – peripheral vascular disease; TIA: transient ischaemic attack.

3.7.2 Dependent

The dependent variable is defined as the variable to be measured. The primary dependent variable of interest was the adverse clinical outcome of all-cause mortality, as this study aims to investigate whether mortality differs by frailty status, and if there is an additional difference

by cardiovascular admission. Both databases contain built-in data on all-cause mortality, detected on the discharge level for each individual discharge. This data represents crucial information collected directly from the discharge records. There are no methods for adjudicating this event and there are no data on the specific cause of death.

3.7.3 Confounders

Confounding variables are related to the independent and dependent variables. These variables can explain the relationship between the independent and dependent variables and therefore must be accounted for in the analysis to assess the true relationship between CVD and frailty. The databases used in this thesis cover a wide range of information such as demographics, medical history and comorbidities that can be classed as confounders.

Demographic information related to the patient include are age, sex, race, median household income and primary expected payer. Demographic information related to the hospital include, location, teaching status and bed size. Demographic information adjusted for in this analysis thesis where available were age, sex, race, weekend admission, primary expected payer, median household income, bed size of hospital, region of hospital, location/teaching status of hospital.

Cardiovascular medical history was included among covariates due to their strong association with recurrent cardiovascular events and higher likelihood of mortality. The exemplary conditions that were used as covariates include smoking status, previous AMI, previous percutaneous coronary intervention (PCI), previous coronary artery bypass graft (CABG) and dyslipidaemia.

Comorbidities included in the NIS are numerous and are dependent on the granularity of the ICD codes. The most commonly evaluated comorbidities in the cardiovascular studies

evaluating NIS and NEDS include: cardiovascular (HF, PVD, valvular heart disease, hypertension), respiratory (chronic lung disease, pulmonary circulation disorders), endocrine (hypothyroidism, diabetes mellitus), renal (fluid and electrolyte disorders, renal failure) psychiatric (depression, psychosis, substance misuse, alcoholism), oncological (metastatic cancer, solid tumours with no metastasis), haematological (anaemia, coagulopathies, thrombocytopaenia), gastrointestinal (liver disease, peptic ulcer disease), infectious (acquired immune deficiency syndrome (AIDS)), neurological and other (e.g. dementia, weight loss, obesity).

Each comorbidity is coded as a binary variable and is identified using ICD-10-CM codes. This thesis used the following comorbidities based on availability within the NIS, lack of inclusion in the HFRS, clinical knowledge and the supervisory team: anaemias, coagulopathy, diabetes mellitus, liver disease, metastatic cancer, PVD, and chronic renal failure **(Table** 3.3**)**.

3.8 Analysis

3.8.1 Overview

All statistical analyses were weighted and performed using the SPSS version 27 (IBM Corp, Armonk, NY) [155]. As described, this thesis uses two datasets and therefore, the results section of this thesis describes specific aspects of the methodology of each study in detail. This section aims to provide an overview of the general methodology and the statistical methods.

3.8.2 Data preparation

Prior to starting each study, the datasets were critically examined for completeness, the presence of inconsistencies and any limitations of data analysis by general inspection and cross-tabulation of the dataset. Each major variable to this study was checked using frequency

statistics and their upper and lower bounds. Cases were excluded if they did not meet the inclusion criteria, for instance hospital episodes recorded for patients under 18. As regression analyses were to be performed, cases with missing data for relevant variables were excluded, such as hospital information and patient-related factors. Each study outlined in the results chapter reports which variables were specifically addressed.

3.8.3 Descriptive statistics

Following initial frequency statistics and data cleansing, the total number of admissions were identified and stratified according to their HFRS score into the 3 groups (low, intermediate, and high). The specified variable to be included in the study were finalised from literature searches, clinical knowledge, and the supervisors.

The normality continuous variables were visually checked using Q-Q plots and the Shapiro-Wilk test. Data for continuous variables such as age, length of stay and total charges were summarised using median and interquartile range (IQR) due to being not normally distributed. Categorical variables were compared using the Pearson Chi-squared (X^2) test and summarised as percentages (%), as were ordinal variables. As both datasets are large, specific results of clinical relevance and association were described in preference to every result which yielded a p-value of less than 0.05.

3.8.4 Regression analysis

Logistic regression is a type of regression analysis that was developed as an extension of linear regression [156]. It is a statistical method beneficial when there are multiple co-variables that can affect an outcome. The purpose of logistic regression is to mathematically model a relationship between the independent and dependent variables. The dependent variable is binary so the logistic regression model must be binomial. It has several advantages. Firstly,

logistic regression studies allow control for confounding variables through the ability to examine multiple covariates simultaneously. Secondly the aOR produced from logistic regression can be easily understood and interpreted, allowing conclusions from results to be made. Finally, the model provides an association as well as the direction of association. There are multiple assumptions to consider. Firstly, logistic regression models assume linearity between the dependent and independent variable and cannot assume a curved relationship. Secondly, this model assumes observations are independent and unrelated to each other. Thirdly, data must be pre-processed and cleaned as the model cannot remove null data without decreasing validity. Finally, more variables lead to a decreased reliability of the regression model.

The main outcome investigated as part of the aim of this thesis was all-cause mortality. All-cause mortality is a binary variable, therefore binomial multivariable logistic regression was performed to determine the adjusted odds ratio (aOR) for the outcome (all-cause mortality) of the studied population, using the low frailty group as the reference group. When determining which variables were included as covariates, the clinical and prognostic value of each variable was considered in relation to frailty, all-cause mortality and other independent variables. Having in mind the large sample size, all relevant variables were included in the adjusted analysis to account for confounders, without risk for model overfitting. 77All results were presented as adjusted odds ratios (aOR) with 95% confidence intervals (CI). Results were determined significant at the level of $p<0.05$.

3.9 Ethical approval

The studies included in this thesis did not require ethical approval from an institutional review board. The NEDS and NIS are publicly available national datasets that are anonymised and do not contain any patient-identifiable information.

3.10 Chapter summary

This chapter explored the general methods used in the studies that are outlined in Chapter 4. This chapter provided an overview of the national US databases used in each study, the NEDS and NIS, exploring their general strengths and limitations. This chapter identified the fundamental variables of this thesis, frailty, and the CVD diagnoses of interest (independent), mortality (dependent) and demographics, medical history, and comorbidities (confounders). Finally, this chapter summarised how the general analysis was conducted, with continuous variables summarised using median and IQR, categorical variables compared using X^2 and summarised as percentages, and logistic regression models using aOR of mortality. The following chapter will explore each individual study in further detail, including the results.

4. Chapter 4: Results

4.1 Chapter overview

Chapter 1 and Chapter 2 of this thesis established the need for the studies described in this chapter. The proportion of the population living with CVD and frailty is increasing, CVD and frailty is associated with adverse outcomes, and CVD and frailty are closely related. Frailty is defined as an impairment of multiple systems resulting in an increased vulnerability to stress, leading to an increased risk of adverse outcomes such as hospitalisations and mortality, and is strongly associated with age [4]. With the growing numbers of the elderly population, the proportion of individuals living with frailty in society and across healthcare systems is increasing [3]. Similarly, the numbers of patients living with cardiovascular disease (CVD) is increasing, particularly given an improved survivorship in patients with acute or chronic CVD [157]. The relationship between frailty and CVD is bidirectional [20]. CVD is associated with a three-fold increase in frailty and frailty is independently associated with an increased mortality from CVD [21, 22]. A recent meta-analysis including 31,343 CVD patients reported that the prevalence of frailty was 17.9% and was associated with an increased risk of HF [16].

This chapter provides a broad summary of the results of this thesis pertaining to the aims outlined in Chapter 1 and Chapter 2 and the methods outlined in Chapter 3. It describes the results of each of the two studies conducted: the association between frailty and CVD in the ED, and the association between frailty and CVD in hospital admissions.

4.2 Emergency encounters

4.2.1 Introduction

To investigate the aims of this thesis on a population level, this first study addresses the relationship between CVD and frailty in the ED. As stated previously, whilst there are studies that describe the association between CVD and frailty in the community inpatient setting, there remains little data on whether CVD admissions vary by frailty status in the emergency setting [102, 158]. Inpatient hospitalisations alone may not provide enough information on the associations between frailty and CVD encounters. The ED is an area where patients can be treated and discharged, referred to another department for further care, or die during the encounter. It is essential to know the types of CVD and outcomes of frail patients in the ED as this allows ED services to meet the needs of the growing frail population. Therefore, the aim of this study was to describe the prevalence, clinical characteristics, and mortality of patients admitted with the CVD diagnoses stratified by frailty status. The findings from this study have been submitted for publication **(Appendix 11)**.

4.2.2 Methods

The general methods have been described in Chapter 3. Briefly, the NEDS was used for this initial study. The NEDS provides accurate estimates of all hospital-owned ED encounters in the US. Weighted, the NEDS contains information from approximately 145 million ED encounters. Patients demographics, outcomes, and comorbidities are all captured using ICD-10-CM codes [142].

ICD-10-CM codes were used to identify all adult discharge records with a principal diagnosis of an acute CVD admission between 2016 and 2018. This sample was filtered by the 7 CVD

admissions of interest: AMI, AF, acute ischaemic stroke, HF, PE, cardiac arrest, and acute haemorrhagic stroke. The sample was then stratified according to their frailty status measured by the HFRS into 3 groups: low risk (HFRS <5), intermediate risk (HFRS 5 to 15) and high risk (HFRS >15) [10]. The HFRS was created by identifying a cohort of elderly patients admitted for diagnoses associated with frailty were identified using ICD-10-CM codes [10]. Using the 109 variables included in the final score, patients were grouped into low risk (HFRS <5), intermediate risk (HFRS 5-15) and high risk (HFRS >15) [10]. The HFRS was validated using a local and national cohort in the United Kingdom [10].

Cases were excluded due to missing data for the following variables: age, sex and mortality. As this was an observational study, it was appraised according to the *Strengthening The Reporting of OBservational Studies in Epidemiology* (STROBE) recommendations **(Appendix 12)**.

Continuous variables including age, length of stay and total charges were summarised using median and interquartile ranges (IQR). Categorical variables were compared using the Chi-squared (X^2) test and summarised as percentages (%). Multivariable logistic regression was performed to determine the adjusted odds ratio (aOR) for all-cause mortality. Results were presented as aOR with 95% confidence intervals (CI) and determined significant at the level of $p<0.05$. Regression was adjusted for the following variables: age, sex, race, weekend admission, primary expected payer, median household income, bed size of hospital, region of hospital, location/teaching status of hospital, smoking status, previous AMI, previous percutaneous coronary intervention (PCI), previous coronary artery bypass graft (CABG), dyslipidaemia, and Elixhauser comorbidities (anaemias, coagulopathy, diabetes mellitus, liver disease, metastatic cancer, PVD and chronic renal failure). All statistical analyses were weighted and performed using SPSS version 27 (IBM Corp, Armonk, NY) [155].

4.2.3 Results

4.2.3.1 Cohort characteristics

20,690,808 ED encounters were recorded between 2016 and 2018. After exclusion of missing data for age, sex and all-cause mortality (0.19%) and patients younger than 18 (1.34%), there were 20,498,939 encounters **(Figure** 4.1**)**. 13,520,067 (66.0%) had a low HFRS of <5, 6,384,446 (31.1%) had an intermediate HFRS of 5-15 and 594,426 (2.9%) had a high HFRS of >15. Patients with a high HFRS were more likely to have a higher prevalence of comorbidities such as dyslipidaemia (55.2% for high HFRS vs 53.9% for intermediate HFRS and 29.5% for low HFRS), thrombocytopaenia (6.8% for high HFRS vs 5.6% for intermediate HFRS and 1.3% for low HFRS), anaemia (30.8% for high HFRS vs 30.0% for intermediate HFRS and 6.7% for low HFRS), coagulopathy (9.5% for high HFRS vs 7.5% for intermediate HFRS and 2.0% for low HFRS) and peripheral vascular disease (4.8% for high HFRS vs 4.6% for intermediate HFRS and 1.2% for low HFRS), compared to patients with a low and intermediate HFRS (all p<0.001) **(Table** 4.1**).**

Figure 4.1 Flow diagram of the Emergency Department cohort selection process.

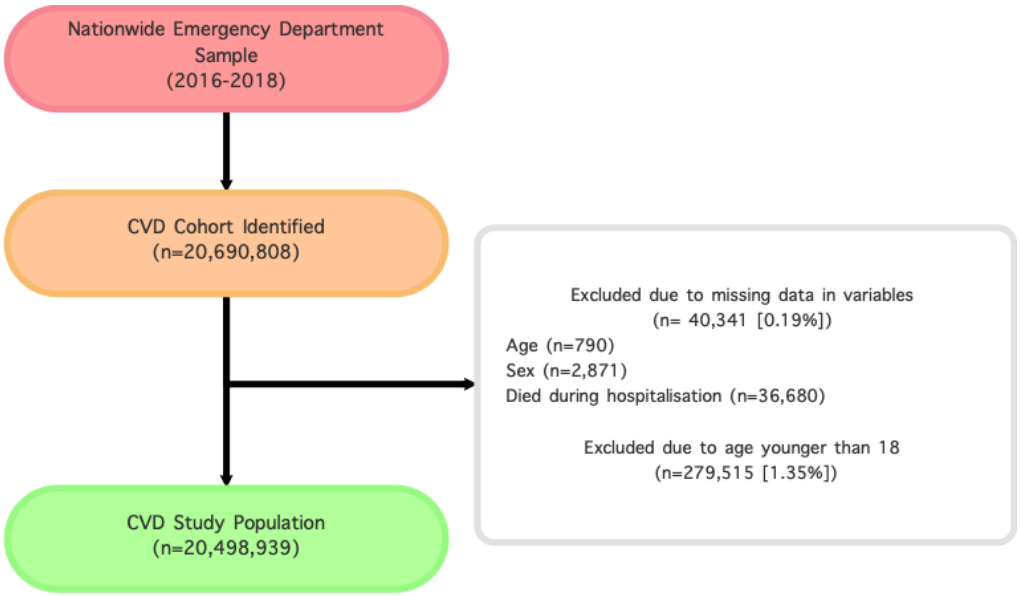


Table 4.1 Patient characteristics for all ED cardiovascular admissions according to HFRS.

Characteristics	Hospital Frailty Risk Score			*p*-value
	Low <5 (66.0%)	Intermediate 5-15 (31.1%)	High >15 (2.9%)	
Number of weighted discharges	13,520,067	6,384,446	594,426	
Age (years), median (IQR)	66 (55, 77)	73 (62, 82)	77 (67, 86)	<0.001
Female sex, %	47.9	49.5	55.4	<0.001
Weekend admission, %	24.4	24.8	25.9	<0.001
Primary expected payer, %				<0.001
Medicare	22.4	61.2	81.1	
Medicaid	27.5	14.2	7.7	
Private Insurance	30.4	16.9	8.5	
Self-pay	14.6	4.9	1.3	
No charge	0.5	0.3	0.1	
Other	4.5	2.5	1.4	
Median Household Income (percentile), %				<0.001
0-25th	35.7	32.4	29.8	
26th–50th	27.5	26.6	25.2	
51st-75th	20.8	22.1	22.8	
76th–100th	16.0	18.9	22.2	
Comorbidities, %				
Dyslipidaemia	29.5	53.9	55.2	<0.001
Thrombocytopenia	1.3	5.6	6.8	<0.001
Smoking	12.5	11.6	9.2	<0.001
Previous AMI	7.1	13.1	9.6	<0.001
Previous PCI	7.1	12.2	7.8	<0.001
Previous CABG	5.3	11.1	7.7	<0.001
Anaemias	6.7	30.0	30.8	<0.001
Valvular disease	5.4	16.2	14.6	<0.001
Peripheral vascular disease	1.2	4.6	4.8	<0.001

Characteristics	Hospital Frailty Risk Score			*p*-value
	Low <5 (66.0%)	Intermediate 5-15 (31.1%)	High >15 (2.9%)	
Coagulopathy	2.0	7.5	9.5	<0.001
Diabetes Mellitus	23.7	43.4	41.0	<0.001
Liver disease	1.2	3.9	3.3	<0.001
Chronic renal failure	10.1	44.0	43.2	<0.001
Chronic pulmonary disease	10.5	26.4	21.6	<0.001
Cancer	2.4	5.4	5.1	<0.001
Hospital Region, %				<0.001
Northeast	16.9	17.6	18.1	
Midwest	22.0	22.9	25.1	
South	42.9	41.9	39.8	
West	18.3	17.6	17.0	
Location/teaching status of hospital, %				<0.001
Rural	26.9	24.8	20.9	
Urban non-teaching	55.7	64.7	71.9	
Urban teaching	17.4	10.5	7.2	
Length of stay (days), median (IQR)	2 (2, 4)	4 (2, 7)	6 (4, 11)	<0.001
Total ED charges (USD), median (IQR)	32,466 (17,930, 61,860)	39,727 (22,524, 74,794)	60,543 (33,013, 119,808)	<0.001
All-cause mortality, %				<0.001
ED all-cause mortality	3.1	0.4	0.1	
In-hospital all-cause mortality	0.4	3.8	8.3	
Overall all-cause mortality	3.5	4.2	8.4	

4.2.3.2 Cause of admission

The most common cause of admission was for 'other CVD' (57.9%), followed by AF (10.2%), AMI (8.8%), acute ischaemic stroke (8.2%), HF (7.3%), PE (3.1%), cardiac arrest (2.4%) and acute haemorrhagic stroke (2.3%). Of the CVD of interest, the cohort admitted with ischaemic stroke had the highest proportion of patients with a high HFRS (16.7%), followed by acute haemorrhagic stroke (10.6%) and AMI (1.7%). The cohort admitted with acute ischaemic stroke had the highest proportion of patients with an intermediate HFRS (57.5%), followed by acute haemorrhagic stroke (42.6%) and HF (40.5%). The cohort admitted with cardiac arrest had the highest proportion of patients with a low HFRS (89.1%), followed by AF (75.2%) and HF (57.8%) **(Table** 4.2 and

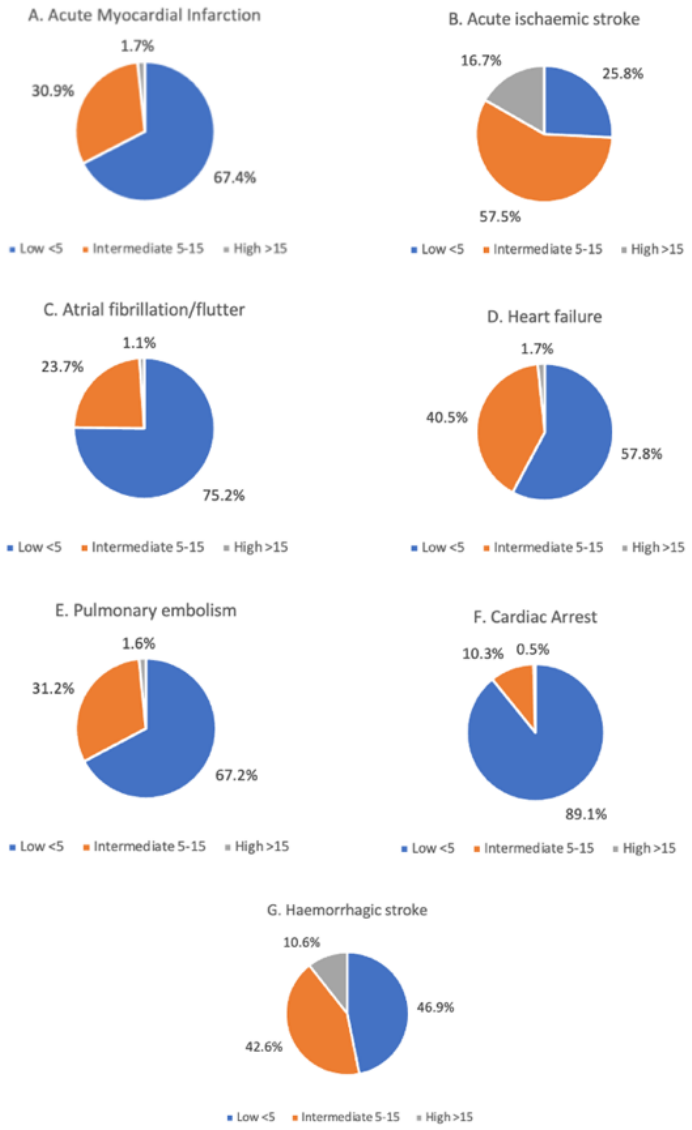
Figure 4.2)**.**

Table 4.2 Prevalence of the ED cardiovascular admission diagnoses within each HFRS category and associated mortality within each CVD admission group.

Admission diagnosis		Hospital Frailty Risk Score			*p*-value
		Low <5 (66.0%)	Intermediate 5-15 (31.1%)	High >15 (2.9%)	
Acute myocardial infarction (N =1,796,127)	**Prevalence**	9.0	8.7	5.0	<0.001
	ED mortality	0.8	0.3	0.1	<0.001
	Overall mortality	1.9	8.9	14.5	<0.001
Ischaemic stroke (N =1,662,442)	**Prevalence**	3.2	15.1	46.7	<0.001
	ED mortality	0.2	<0.1	<0.1	<0.001
	Overall mortality	0.6	2.6	7.4	<0.001
Atrial fibrillation/flutter (N =2,056,294)	**Prevalence**	11.5	7.7	3.7	<0.001
	ED mortality	<0.1	0.1	<0.1	<0.001
	Overall mortality	0.1	1.5	5.9	<0.001
Heart failure (N =1,483,837)	**Prevalence**	6.4	9.5	4.2	<0.001
	ED mortality	0.2	0.1	<0.1	<0.001
	Overall mortality	0.5	3.3	9.1	<0.001
Pulmonary Embolism (N=627,547)	**Prevalence**	3.1	3.1	1.6	<0.001
	ED mortality	0.3	0.1	<0.1	<0.001
	Overall mortality	0.8	5.4	10.7	<0.001
Cardiac arrest (N=495,406)	**Prevalence**	3.3	0.8	0.5	<0.001
	ED mortality	88.2	39.4	5.7	<0.001
	Overall mortality	89.2	78.0	63.2	<0.001
Haemorrhagic stroke (N =458,987)	**Prevalence**	1.6	3.1	8.2	<0.001
	ED mortality	2.0	0.6	0.1	<0.001
	Overall mortality	7.0	20.1	16.0	<0.001
Other CVD (N =11,773,600)	**Prevalence**	61.9	52.1	30.1	<0.001
	ED mortality	0.1	0.1	<0.1	<0.001
	Overall mortality	0.1	2.3	5.9	<0.001

Abbreviations: CVD- Cardiovascular Disease – Emergency Department.

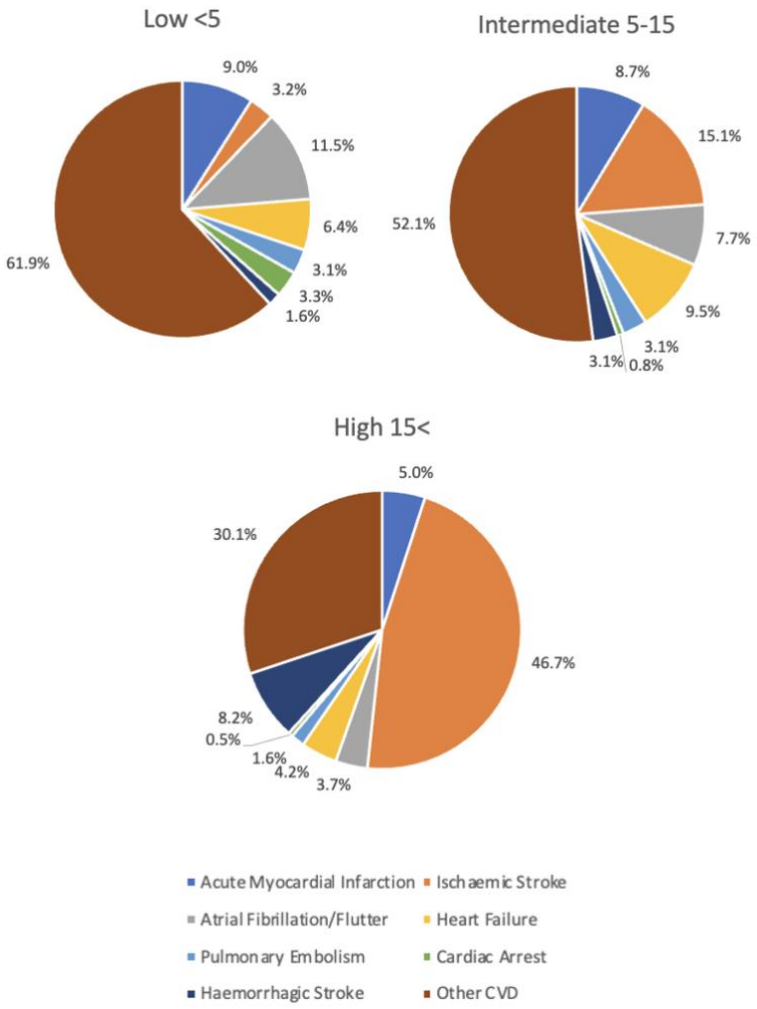
Figure 4.2 Distribution of each HFRS category within each of the selected ED cardiovascular admission causes.



Of the CVD of interest, Ischaemic stroke was the most common cause of encounter for the high HFRS group (46.7%), followed by acute haemorrhagic stroke (8.2%) and AMI (5.0%). Ischaemic stroke was also the most common cause of specific CVD admission in the intermediate HFRS group (15.1%), followed by HF (9.5%) and AMI (8.7%). The most common cause of specific CVD encounter in the low HFRS group was AF (11.5%), followed by AMI (9.0%) and HF (6.4%). **(**

Figure 4.3**).**

Figure 4.3 Distribution of selected ED cardiovascular admission causes within each HFRS category.



4.2.3.3 Discharge disposition

Patients with a high HFRS were less likely to be routinely discharged home (1.2% for high HFRS vs 10.4% for intermediate HFRS and 53.2% for low HFRS), transferred to a short-term hospital (0.4% for high HFRS vs 2.4% for intermediate HFRS and 7.3% for low HFRS) and more likely to be admitted to hospital as an inpatient (97.3% for high HFRS vs 84.5% for intermediate HFRS and 33.2% for low HFRS) **(**

Table 4.3).

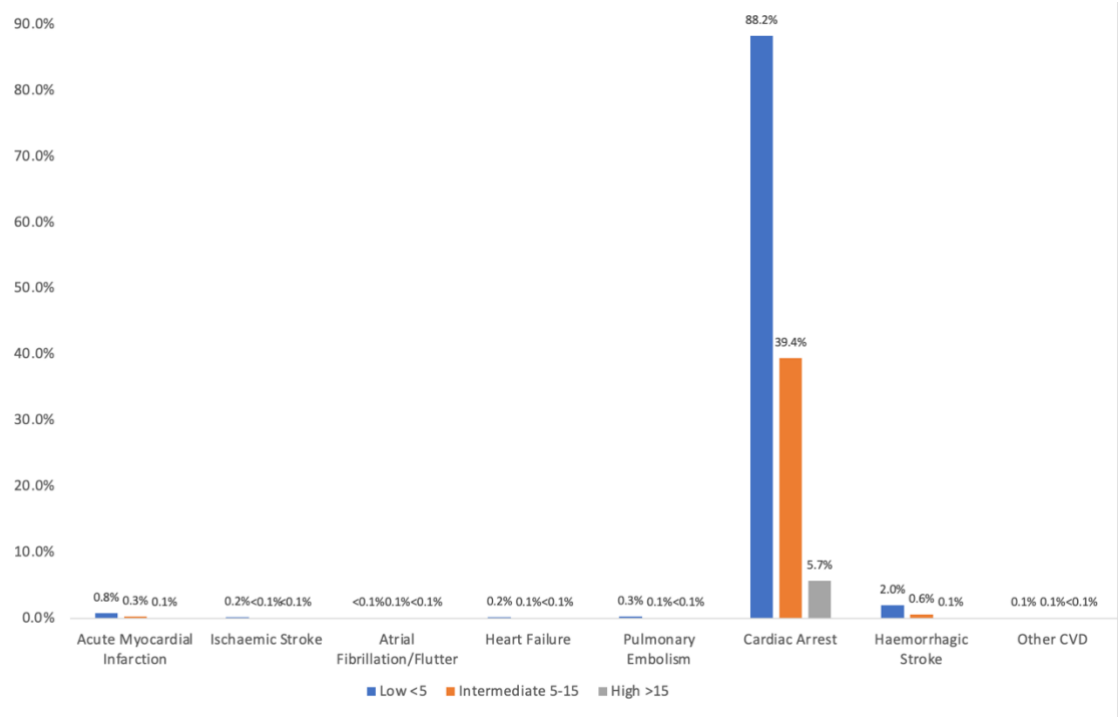
Table 4.3 Destination of discharge from ED stratified by HFRS category.

Characteristics	Hospital Frailty Risk Score			*p*-value
	Low <5 (66.0%)	Intermediate 5-15 (31.1%)	High >15 (2.9%)	
Number of weighted discharges	13,520,067	6,384,446	594,426	
Discharge disposition, %				<0.001
Home	53.2	10.4	1.2	
Transfer to short-term hospital	7.3	2.4	0.4	
Other transfer	1.5	1.2	0.6	
Home health care	0.4	0.8	0.4	
Left against medical advice	1.3	0.3	<0.1	
Admitted as inpatient	33.2	84.5	97.3	
ED mortality	3.1	0.4	0.1	

4.2.3.4 Mortality

Patients with a high HFRS generally had lower unadjusted rates of ED all-cause mortality compared to their lower frailty counterparts (0.1% vs. 0.8% for intermediate HFRS group and 7.9% for low HFRS group, p<0.001). However, high HFRS was associated with increased rates of overall mortality (ED and in-hospital combined mortality) (9.4% vs. 6.3% for intermediate HFRS group and 8.7% for low HFRS group, p<0.001). This trend was observed across all CVD admissions, with lower crude rates of ED all-cause mortality and increased rates of overall mortality with increasing HFRS category (**Table** 4.2**).**

Figure 4.4. ED mortality in different frailty risk categories and cardiovascular admission diagnoses.



On adjustment for baseline covariates, the high HFRS group had a decreased odds of ED mortality for patients admitted with across all CVD admission cohorts ($p<0.001$), compared to their low HFRS counterparts. The intermediate HFRS group also had decreased odds of ED mortality across most CVD admission cohorts (apart from AF), though the effect size was greater for the high HFRS group ($p<0.001$). When looking at the effect size, patients with intermediate and high HFRS admitted for cardiac arrest had the lowest odds of ED all-cause mortality (aOR 0.06, 95% CI 0.04 to 0.11 for high HFRS group and aOR 0.12, 95% CI 0.11 to 0.12 for intermediate HFRS group), compared to their low frailty risk counterparts (**Table** 4.4 and

Figure 4.5).

Apart from cardiac arrest, adjusted odds of overall mortality (combined ED and in-hospital mortality) for the intermediate and high HFRS groups were increased (p<0.001), compared to their low HFRS counterparts. When looking at the effect size, intermediate and high HFRS patients admitted with AF had the highest odds of overall all-cause mortality (aOR 27.14, 95% CI 25.03 to 29.43 for high HFRS group and aOR 8.38, 95% CI 7.91 to 8.89 for intermediate HFRS group), compared to their low frailty risk counterparts (**Table** 4.4 and

Figure 4.5).

Table 4.4 Adjusted odds ratios of ED and overall mortality in different HFRS categories and selected ED cardiovascular admission diagnoses*.

Admission Diagnosis		**Hospital Frailty Risk Score**			
		Intermediate 5-15 (35.5%)		**High >15 (4.8%)**	
		aOR [95%CI]	***p*-value**	**aOR [95% CI]**	***p*-value**
Acute myocardial infarction (N =1,796,127)	**Hospitalisation**	4.47 [4.41-4.54]	<0.001	28.40 [25.09-32.14]	<0.001
	ED mortality	0.41 [0.39-0.44]	<0.001	0.06 [0.04-0.11]	<0.001
	Overall mortality	4.10 [4.02-4.18]	<0.001	5.69 [5.48-5.91]	<0.001
Ischaemic stroke (N =1,662,442)	**Hospitalisation**	5.71 [5.65-5.77]	<0.001	40.35 [39.11-41.63]	<0.001
	ED mortality	0.36 [0.31-0.41]	<0.001	0.12 [0.09-0.16]	<0.001
	Overall mortality	3.83 [3.67-4.00]	<0.001	9.83 [9.42-10.26]	<0.001
Atrial fibrillation/flutter (N =2,056,294)	**Hospitalisation**	4.41 [4.37-4.45]	<0.001	23.22 [21.66-24.89]	<0.001
	ED mortality	1.79 [1.51-2.13]	<0.001	0.11 [0.02-0.79]	<0.001
	Overall mortality	8.38 [7.91-8.89]	<0.001	27.14 [25.03-29.43]	<0.001
Heart failure (N =1,483,837)	**Hospitalisation**	7.06 [6.98-7.13]	<0.001	48.68 [44.12-53.70]	<0.001
	ED mortality	0.74 [0.66-0.84]	<0.001	0.24 [0.11-0.50]	<0.001

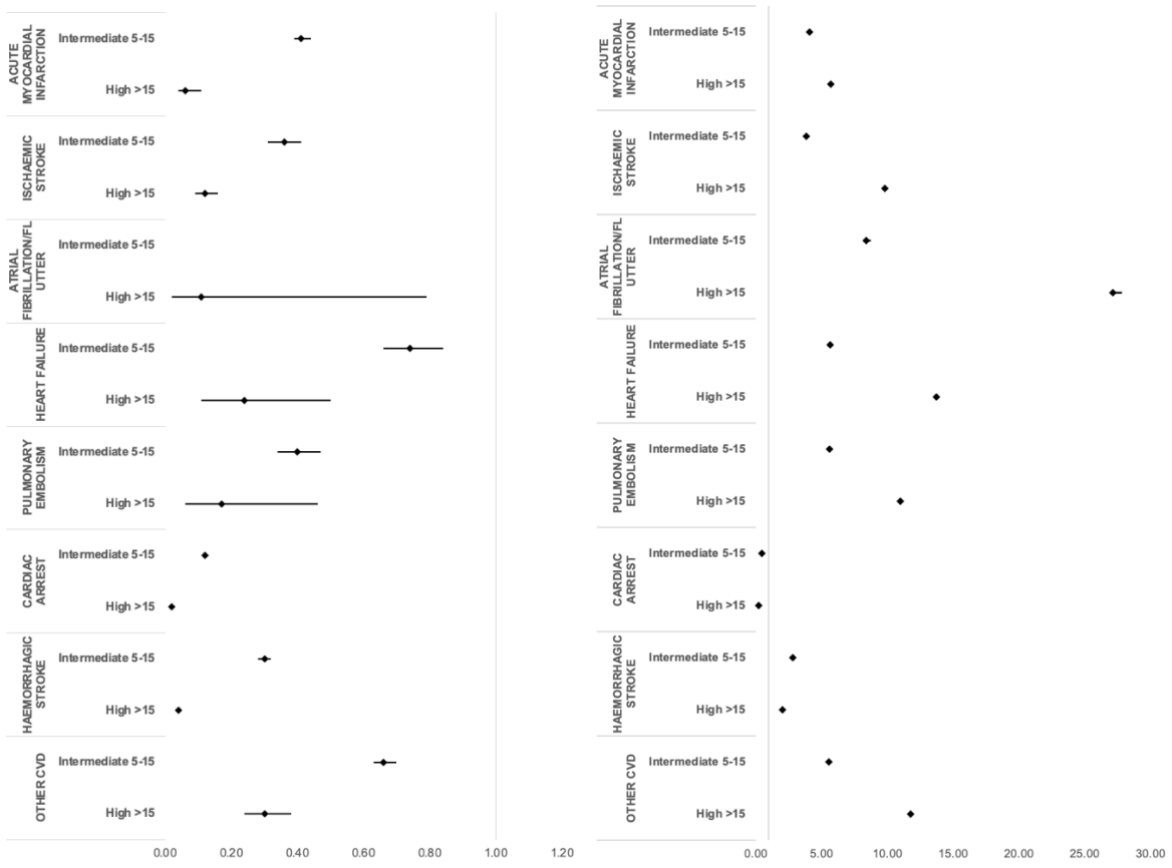
	Overall mortality	5.65 [5.45-5.86]	<0.001	13.71 [12.95-14.51]	<0.001
Pulmonary Embolism (N=627,547)	**Hospitalisation**	4.61 [4.51-4.71]	<0.001	28.44 [22.94-35.26]	<0.001
	ED mortality	0.40 [0.34-0.47]	<0.001	0.17 [0.06-0.46]	<0.001
	Overall mortality	5.61 [5.38-5.86]	<0.001	10.98 [10.16-11.87]	<0.001
Cardiac arrest (N=495,406)	**Hospitalisation**	40.64 [39.22-42.12]	<0.001	42.01 [35.19-49.21]	<0.001
	ED mortality	0.12 [0.11-0.12]	<0.001	0.02 [0.01-0.03]	<0.001
	Overall mortality	0.43 [0.42-0.45]	<0.001	0.20 [0.18-0.22]	<0.001
Haemorrhagic stroke (N =458,987)	**Hospitalisation**	8.35 [8.20-8.50]	<0.001	59.14 [57.32-61.03]	<0.001
	ED mortality	0.30 [0.28-0.32]	<0.001	0.04 [0.03-0.05]	<0.001
	Overall mortality	2.79 [2.73-2.86]	<0.001	2.01 [1.95-2.08]	<0.001
Other CVD (N=11,773,600)	**Hospitalisation**	5.63 [5.61-5.65]	<0.001	24.05 [23.51-24.60]	<0.001
	ED mortality	0.66 [0.63-0.70]	<0.001	0.30 [0.24-0.38]	<0.001
	Overall mortality	5.56 [5.46-5.65]	<0.001	11.75 [11.45-12.06]	<0.001

*Reference group is low HFRS score <5 for each CVD admission diagnosis.

Multivariable logistic regression model adjusted for: age, sex, weekend admission, primary expected payer, median household income, region and teaching status of the hospital, dyslipidaemia, smoking, thrombocytopenia, previous AMI, anaemia, coagulopathies, liver disease, diabetes, hypertension, malignancy, peripheral vascular disease, chronic pulmonary disease, chronic renal disease and valvular heart diseases.

Abbreviations: aOR – adjusted Odds Ratio; CI – Confidence Interval; ED – Emergency Department; HFRS – Hospital Frailty Risk Score.

Figure 4.5. Adjusted ED mortality **(left) and overall mortality (right)** rates for different frailty risk category and selected ED cardiovascular admission causes*.



*Reference group is low HFRS score <5 for each CVD admission diagnosis.

Multivariable logistic regression model adjusted for: age, sex, weekend admission, primary expected payer, median household income, region and teaching status of the hospital, dyslipidaemia, smoking, thrombocytopenia, previous AMI, anaemia, coagulopathies, liver disease, diabetes, hypertension, malignancy, peripheral vascular disease, chronic pulmonary disease, chronic renal disease and valvular heart diseases.

Abbreviations: aOR – adjusted Odds Ratio; CI – Confidence Interval; ED – Emergency Department; HFRS – Hospital Frailty Risk Score.

4.2.3.5 Subgroup analyses

There were 1,796,127 encounters for AMI. 1,210,737 (67.4%) had a high HFRS, 555,343 (30.9%) had an intermediate HFRS and 29,932 (1.7%) had a low HFRS. Patients admitted for AMI with a high HFRS were more likely to be older than those with an intermediate and low HFRS (median age 79 for high HFRS vs 73 for intermediate HFRS and 63 for low HFRS). This was the same for their likelihood of being female (52.9% for high HFRS vs 44.2% for intermediate HFRS and 34.9% for low HFRS). Patients with a high HFRS more comorbid with conditions such as anaemia (40.8% for high HFRS vs 30.6% for intermediate HFRS and 6.8%

for low HFRS), thrombocytopaenia (9.9% for high HFRS vs 7.6% for intermediate HFRS and 2.0% for low HFRS), chronic renal failure (58.2% for high HFRS vs 45.7% for intermediate HFRS and 8.9% for low HFRS) and PVD (6.3% for high HFRS vs 6.2% for intermediate HFRS and 1.8% for low HFRS) compared to patients with a low HFRS (p<0.001) **(Table** 4.5**)**.

Table 4.5 Characteristics of patients presenting with acute myocardial infarction.

Characteristics	Hospital Frailty Risk Score			*p*-value
	Low <5 (67.4%)	Intermediate 5-15 (30.9%)	High >15 (1.7%)	
Number of weighted discharges	1,210,737	555,343	29,932	
Age (years), median (IQR)	63 (55, 73)	73 (63, 82)	79 (70, 87)	<0.001
Female sex, %	34.9	44.2	52.9	<0.001
Weekend admission, %	27.2	27.3	26.4	<0.001
Primary expected payer, %				<0.001
Medicare	47.9	73.0	83.9	
Medicaid	10.2	7.6	5.3	
Private Insurance	31.8	14.2	7.8	
Self-pay	6.7	2.8	1.4	
No charge	0.5	0.3	0.2	
Other	3.0	2.0	1.4	
Median Household Income (percentile), %				<0.001
0-25th	31.5	32.4	31.7	
26th–50th	28.4	26.6	25.5	
51st-75th	21.9	22.2	22.2	
76th–100th	18.3	18.8	20.5	
Homelessness, %	0.3	0.4	0.2	<0.001
Comorbidities, %				
Dyslipidaemia	55.0	65.8	58.8	<0.001
Thrombocytopenia	2.0	7.6	9.9	<0.001
Smoking	22.2	13.4	7.6	<0.001

Characteristics	Hospital Frailty Risk Score			*p*-value
	Low <5 (67.4%)	Intermediate 5-15 (30.9%)	High >15 (1.7%)	
Previous AMI	13.1	18.5	14.2	<0.001
Previous PCI	14.6	18.3	11.7	<0.001
Previous CABG	8.1	13.3	9.9	<0.001
Anaaemias	6.8	30.6	40.8	<0.001
Valvular disease	7.0	18.0	20.8	<0.001
Peripheral vascular disease	1.8	6.2	6.3	<0.001
Coagulopathy	2.5	9.5	12.6	<0.001
Diabetes Mellitus	31.6	49.2	46.7	<0.001
Liver disease	1.3	5.2	6.9	<0.001
Chronic renal failure	8.9	45.7	58.2	<0.001
Chronic pulmonary disease	12.2	25.5	25.1	<0.001
Length of stay (days), median (IQR)	2 (2, 3)	4 (2, 8)	7 (4, 13)	<0.001
Total ED and in-hospital charges (USD), median (IQR)	64,266 (37,412, 100,202)	71,890 (36,099, 139,045)	87,723 (42,721, 182, 812)	<0.001

Abbreviations: AMI – Acute Myocardial Infarction; CABG – Coronary Artery Bypass Graft; ED – Emergency Department; IQR – Interquartile Range; PCI – Percutaneous Coronary Intervention; USD – United States Dollar.

There were 1,662,442 encounters for acute ischaemic stroke. 429,032 (25.8%) had a high HFRS, 955,886 (57.5%) had an intermediate HFRS and 227,212 (16.7%) had a low HFRS. Patients admitted for acute ischaemic stoke with a high HFRS were more likely to be older than those with an intermediate or low HFRS (median age 77 for high HFRS vs 71 for intermediate HFRS and 67 for low HFRS). Patients with a high HFRS were more likely to be female (50.2%for high HFRS vs 49.6% for intermediate HFRS and 46.7% for low HFRS) and more comorbid with conditions such as dyslipidaemia (59.4.2% for high HFRS vs 58.6% for intermediate HFRS and 39.2% for low HFRS), diabetes (40.2% for high HFRS vs 39.0% for intermediate HFRS and 28.4% for low HFRS), chronic pulmonary disease (15.7% for high

HFRS vs 12.5% for intermediate HFRS and 6.8% for low HFRS), liver disease (1.8% for high HFRS vs 1.4% for intermediate HFRS and 0.7% for low HFRS) and valvular disease (10.4% for high HFRS vs 7.7% for intermediate HFRS and 3.6% for low HFRS) compared to patients with a low HFRS (all p<0.001) **(**

Table 4.6).

Table 4.6 Characteristics of patients presenting with acute ischaemic stroke.

Characteristics	Hospital Frailty Risk Score			*p*-value
	Low <5 (25.8%)	**Intermediate 5-15 (57.5%)**	**High >15 (16.7%)**	
Number of weighted discharges	429,032	955,886	277,212	
Age (years), median (IQR)	67 (57, 77)	71 (61, 82)	77 (66, 86)	<0.001
Female sex, %	46.7	49.6	55.2	<0.001
Weekend admission, %	25.0	26.0	26.5	<0.001
Primary expected payer, %				<0.001
Medicare	55.1	66.0	76.7	

Characteristics	Hospital Frailty Risk Score			*p*-value
	Low <5 (25.8%)	Intermediate 5-15 (57.5%)	High >15 (16.7%)	
Medicaid	9.8	9.0	7.8	
Private Insurance	26.0	18.3	11.3	
Self-pay	6.3	4.3	2.5	
No charge	0.3	0.3	0.2	
Other	2.5	2.0	1.5	
Median Household Income (percentile), %				<0.001
0-25th	31.7	31.3	31.0	
26th–50th	28.5	26.6	25.1	
51st-75th	21.9	22.5	23.0	
76th–100th	17.9	19.6	20.9	
Homelessness, %	0.1	0.3	0.4	<0.001
Comorbidities, %				
Dyslipidaemia	39.2	58.6	59.4	<0.001
Thrombocytopenia	1.1	2.7	4.7	<0.001
Smoking	15.1	15.9	11.5	<0.001
Previous AMI	4.4	7.8	8.1	<0.001
Previous PCI	4.2	7.5	7.0	<0.001
Previous CABG	4.0	6.9	6.9	<0.001
Anaemias	3.9	11.5	20.4	<0.001
Valvular disease	3.6	7.7	10.4	<0.001
Peripheral vascular disease	0.8	2.4	3.6	<0.001
Coagulopathy	2.0	4.2	7.0	<0.001
Diabetes Mellitus	28.4	39.0	40.2	<0.001
Liver disease	0.7	1.4	1.8	<0.001
Chronic renal failure	4.6	17.0	30.0	<0.001
Chronic pulmonary disease	6.8	12.5	15.7	<0.001
Length of stay (days), median (IQR)	2 (1, 3)	3 (2, 5)	5 (3, 9)	<0.001

Characteristics	Hospital Frailty Risk Score			*p*-value
	Low <5 (25.8%)	Intermediate 5-15 (57.5%)	High >15 (16.7%)	
Total ED and in-hospital charges (USD), median (IQR)	31,338 (20,350, 49,857)	39,490 (24,355, 67,104)	58,132 (32,803, 108,342)	<0.001

Abbreviations: AMI – Acute Myocardial Infarction; CABG – Coronary Artery Bypass Graft; ED – Emergency Department; IQR – Interquartile Range; PCI – Percutaneous Coronary Intervention; USD – United States Dollar.

There were 2,056,294 encounters for AF. 1,546,361 (75.2%) had a high HFRS, 487,734 (23.7%) had an intermediate HFRS and 21,710 (1.1%) had a low HFRS. Patients admitted for AF with a high HFRS were more likely to be older than those with an intermediate or low HFRS (median age 82 for high HFRS vs 76 for intermediate HFRS and 69 for low HFRS) and more likely to be female (63.8%for high HFRS vs 55.3% for intermediate HFRS and 47.3% for low HFRS). High HFRS patients we more comorbid with conditions such as thrombocytopaenia (7.4% for high HFRS vs 4.9% for intermediate HFRS and 1.3% for low HFRS), liver disease (4.1% for high HFRS vs 3.1% for intermediate HFRS and 1.0% for low HFRS), anaemias (32.1% for high HFRS vs 23.0% for intermediate HFRS and 5.3% for low HFRS), PVD (2.5% for high HFRS vs 2.3% for intermediate HFRS and 0.5% for low HFRS) and valvular disease (22.5% for high HFRS vs 19.5% for intermediate HFRS and 8.5% for low HFRS) compared to patients with a low HFRS (all p<0.001) **(Table** 4.7**)**.

Table 4.7 Characteristics of patients presenting with atrial fibrillation/flutter.

Characteristics	Hospital Frailty Risk Score			*p*-value
	Low <5 (75.2%)	Intermediate 5-15 (23.7%)	High >15 (1.1%)	
Number of weighted discharges	1,546,361	487,734	21,710	
Age (years), median (IQR)	69 (59, 78)	76 (67, 84)	82 (75, 88)	<0.001

Characteristics	Hospital Frailty Risk Score			*p*-value
	Low <5 (75.2%)	Intermediate 5-15 (23.7%)	High >15 (1.1%)	
Female sex, %	47.3	55.3	63.8	<0.001
Weekend admission, %	23.9	23.5	24.2	<0.001
Primary expected payer, %				<0.001
Medicare	59.8	79.0	89.5	
Medicaid	6.6	5.4	2.8	
Private Insurance	27.6	12.2	5.7	
Self-pay	3.4	1.7	0.7	
No charge	0.2	0.1	<0.1	
Other	2.4	1.5	1.2	
Median Household Income (percentile), %				<0.001
0-25th	25.5	28.7	27.8	
26th–50th	27.4	27.0	25.2	
51st-75th	24.5	23.5	24.2	
76th–100th	22.6	20.7	22.8	
Homelessness, %	0.3	0.6	0.3	<0.001
Comorbidities, %				
Dyslipidaemia	33.9	53.1	51.1	<0.001
Thrombocytopenia	1.3	4.9	7.4	<0.001
Smoking	8.5	8.5	5.4	<0.001
Previous AMI	5.5	10.3	9.2	<0.001
Previous PCI	5.8	10.2	7.5	<0.001
Previous CABG	4.6	8.4	6.6	<0.001
Anaemias	5.3	23.0	32.1	<0.001
Valvular disease	8.5	19.5	22.5	<0.001
Peripheral vascular disease	0.5	2.3	2.5	<0.001
Coagulopathy	2.0	6.5	10.0	<0.001
Diabetes Mellitus	20.0	33.1	31.9	<0.001
Liver disease	1.0	3.1	4.1	<0.001

Characteristics	Hospital Frailty Risk Score			*p*-value
	Low <5 (75.2%)	Intermediate 5-15 (23.7%)	High >15 (1.1%)	
Chronic renal failure	6.6	32.7	45.1	<0.001
Chronic pulmonary disease	11.8	27.2	26.7	<0.001
Length of stay (days), median (IQR)	2 (1, 3)	3 (2, 6)	6 (4, 9)	<0.001
Total ED and in-hospital charges (USD), median (IQR)	21,552 (12,381, 36,053)	29,965 (17,898, 52,761)	43,833 (26,340, 80,853)	<0.001

Abbreviations: AMI – Acute Myocardial Infarction; CABG – Coronary Artery Bypass Graft; ED – Emergency Department; IQR – Interquartile Range; PCI – Percutaneous Coronary Intervention; USD – United States Dollar.

There were 1,483,837 encounters for HF. 857,682 (57.8%) had a high HFRS, 601,133 (40.5%) had an intermediate HFRS and 24,673 (1.7%) had a low HFRS. Patients admitted for AF with a high HFRS were more likely to be older than those with an intermediate and low HFRS (median age 81 for high HFRS vs 76 for intermediate HFRS and 69 for low HFRS). Patients with a high HFRS were more likely to be female (58.3% for high HFRS vs 49.9% for intermediate HFRS and 45.5% for low HFRS) and more comorbid with conditions such as thrombocytopaenia (9.5% for high HFRS vs 6.1% for intermediate HFRS and 1.9% for low HFRS), liver disease (4.6% for high HFRS vs 4.3% for intermediate HFRS and 1.9% for low HFRS), anaemias (45.6% for high HFRS vs 35.8% for intermediate HFRS and 12.5% for low HFRS) and PVD (2.9% for high HFRS vs 2.4% for intermediate HFRS and 0.8% for low HFRS) compared to patients with a low HFRS (all p<0.001) **(**

Table 4.8**)**.

Table 4.8 Characteristics of patients presenting with heart failure.

Characteristics	Hospital Frailty Risk Score			*p*-value
	Low <5 (57.8%)	Intermediate 5-15 (40.5%)	High >15 (1.7%)	
Number of weighted discharges	857,682	601,133	24,673	
Age (years), median (IQR)	69 (57, 82)	76 (64, 85)	81 (72, 88)	<0.001
Female sex, %	45.5	49.9	58.3	<0.001
Weekend admission, %	25.3	25.1	25.7	<0.001
Primary expected payer, %				<0.001
Medicare	65.2	77.5	86.0	
Medicaid	13.7	8.9	5.3	
Private Insurance	13.8	9.9	6.6	
Self-pay	4.7	1.9	0.9	
No charge	0.3	0.1	0.1	
Other	2.3	1.7	1.1	
Median Household Income (percentile), %				<0.001
0-25th	37.6	33.0	29.1	
26th–50th	28.6	26.6	26.2	
51st-75th	19.8	21.9	22.4	
76th–100th	14.0	18.5	22.3	
Homelessness, %	0.8	0.8	0.4	<0.001
Comorbidities, %				
Dyslipidaemia	30.3	50.1	48.6	<0.001
Thrombocytopenia	1.9	6.1	9.5	<0.001
Smoking	12.3	10.2	4.7	<0.001
Previous AMI	10.6	16.0	14.5	<0.001
Previous PCI	8.2	13.3	10.1	<0.001
Previous CABG	10.0	15.4	12.2	<0.001
Anaemias	12.5	35.8	45.6	<0.001

Characteristics	Hospital Frailty Risk Score			*p*-value
	Low <5 (57.8%)	Intermediate 5-15 (40.5%)	High >15 (1.7%)	
Valvular disease	12.2	25.6	29.2	<0.001
Peripheral vascular disease	0.8	2.4	2.9	<0.001
Coagulopathy	2.4	7.6	11.9	<0.001
Diabetes Mellitus	33.7	46.3	44.3	<0.001
Liver disease	1.9	4.3	4.6	<0.001
Chronic renal failure	17.1	52.6	66.9	<0.001
Chronic pulmonary disease	24.1	41.4	41.0	
Length of stay (days), median (IQR)	3 (2, 4)	4 (3, 7)	7 (5, 12)	<0.001
Total ED and in-hospital charges (USD), median (IQR)	24,150 (14,639, 40,737)	33,388 (19,700, 59,088)	54,783 (29,946, 102,563)	<0.001

Abbreviations: AMI – Acute Myocardial Infarction; CABG – Coronary Artery Bypass Graft; ED – Emergency Department; IQR – Interquartile Range; PCI – Percutaneous Coronary Intervention; USD – United States Dollar.

There were 627,547 encounters for PE. 421,229 (67.2%) had a high HFRS, 195,479 (31.2%) had an intermediate HFRS and 9,781 (1.6%) had a low HFRS. Patients admitted for PE with a high HFRS were more likely to be older than those with an intermediate and low HFRS (median age 78 for high HFRS vs 70 for intermediate HFRS and 60 for low HFRS). Patients with a high HFRS were more likely to be female (60.5% for high HFRS vs 55.2% for intermediate HFRS and 50.5% for low HFRS) and more comorbid with conditions such as dyslipidaemia (44.5% for high HFRS vs 42.6% for intermediate HFRS and 26.2% for low HFRS), diabetes (29.6% for high HFRS vs 28.8% for intermediate HFRS and 16.6% for low HFRS), chronic pulmonary disease (28.1% for high HFRS vs 27.8% for intermediate HFRS and 12.6% for low HFRS), and anaemias (38.6% for high HFRS vs 28.5% for intermediate HFRS and 11.8% for low HFRS) compared to patients with a low HFRS (all p<0.001) **(**

Table 4.9**)**.

Table 4.9 Characteristics of patients presenting with pulmonary embolism.

Characteristics	Hospital Frailty Risk Score			*p*-value
	Low <5 (67.2%)	**Intermediate 5-15 (31.2%)**	**High >15 (1.6%)**	
Number of weighted discharges	421,229	195,479	9,781	
Age (years), median (IQR)	60 (47, 71)	70 (59, 80)	78 (68, 85)	<0.001
Female sex, %	50.5	55.2	60.5	<0.001
Weekend admission, %	65.9	32.4	1.7	<0.001
Primary expected payer, %				<0.001
Medicare	40.2	66.6	79.9	
Medicaid	14.0	10.0	6.9	
Private Insurance	37.0	18.7	10.7	
Self-pay	5.3	2.7	0.9	
No charge	0.4	0.2	0.1	
Other	3.1	1.9	1.5	
Median Household Income (percentile), %				<0.001
0-25th	27.8	29.4	27.0	
26th–50th	27.0	26.1	25.0	
51st-75th	23.9	24.0	23.0	
76th–100th	21.2	20.6	25.0	
Homelessness, %	0.6	0.8	0.2	<0.001
Comorbidities, %				
Dyslipidaemia	26.2	42.6	44.5	<0.001
Thrombocytopenia	2.8	7.7	9.9	<0.001
Smoking	13.4	10.7	5.9	<0.001

Characteristics	Hospital Frailty Risk Score			*p*-value
	Low <5 (67.2%)	Intermediate 5-15 (31.2%)	High >15 (1.6%)	
Previous AMI	3.6	7.1	6.3	<0.001
Previous PCI	3.5	6.2	5.5	<0.001
Previous CABG	2.3	4.3	3.0	<0.001
Anaemias	11.8	28.5	38.6	<0.001
Valvular disease	3.4	8.2	10.3	<0.001
Peripheral vascular disease	0.4	1.5	2.3	<0.001
Coagulopathy	7.3	13.1	15.6	<0.001
Diabetes Mellitus	16.6	28.8	29.6	<0.001
Liver disease	2.0	4.4	5.5	<0.001
Chronic renal failure	4.5	23.4	37.1	<0.001
Chronic pulmonary disease	12.6	27.8	28.1	<0.001
Length of stay (days), median (IQR)	3 (2, 4)	4 (3, 7)	7 (4, 11)	<0.001
Total ED and in-hospital charges (USD), median (IQR)	25,714 (16,266, 42,702)	41,040 (24,310, 72,495)	63,254 (37,499, 115,130)	<0.001

Abbreviations: AMI – Acute Myocardial Infarction; CABG – Coronary Artery Bypass Graft; ED – Emergency Department; IQR – Interquartile Range; PCI – Percutaneous Coronary Intervention; USD – United States Dollar.

There were 495,406 encounters for cardiac arrest. 440,834 (89.1%) had a high HFRS, 50,997 (10.3%) had an intermediate HFRS and 2,689 (0.5%) had a low HFRS. Patients admitted for cardiac arrest with a high HFRS were more likely to be older than those with an intermediate and low HFRS (median age 70 for high HFRS vs 67 for intermediate HFRS and 69 for low HFRS). Patients with a high HFRS were less likely to be female (45.4% for high HFRS vs 44.3% for intermediate HFRS and 37.8% for low HFRS) and more comorbid with conditions such as dyslipidaemia (34.1% for high HFRS vs 29.5% for intermediate HFRS and 9.3% for low HFRS), diabetes (40.7% for high HFRS vs 39.0% for intermediate HFRS and 18.3% for

low HFRS), chronic pulmonary disease (24.7% for high HFRS vs 22.1% for intermediate HFRS and 8.3% for low HFRS), and PVD (4.5% for high HFRS vs 2.4% for intermediate HFRS and 0.2% for low HFRS) compared to patients with a low HFRS (all p<0.001) **(**

Table 4.10**)**.

Table 4.10 Characteristics of patients presenting with cardiac arrest.

Characteristics	**Hospital Frailty Risk Score**			***p*-value**
	Low <5 (89.1%)	**Intermediate 5-15 (10.3%)**	**High >15 (0.5%)**	
Number of weighted discharges	440,834	50,997	2,689	
Age (years), median (IQR)	69 (57, 80)	67 (56, 77)	70 (59, 79)	<0.001
Female sex, %	37.8	44.3	45.4	<0.001
Weekend admission, %	29.7	28.3	25.5	<0.001
Primary expected payer, %				<0.001
Medicare	54.7	65.9	66.1	
Medicaid	10.5	11.0	14.5	
Private Insurance	18.3	14.6	12.5	
Self-pay	13.4	5.7	3.8	
No charge	0.3	0.2	<0.1	
Other	2.9	2.6	3.2	
Median Household Income (percentile), %				<0.001
0-25th	33.6	34.1	38.6	
26th–50th	26.8	26.6	22.7	
51st-75th	20.9	21.6	20.9	
76th–100th	18.6	17.7	17.8	
Homelessness, %	0.1	0.4	1.3	<0.001
Comorbidities, %				
Dyslipidaemia	9.3	29.5	34.1	<0.001
Thrombocytopenia	0.1	5.2	11.2	<0.001

Characteristics	Hospital Frailty Risk Score			*p*-value
	Low <5 (89.1%)	Intermediate 5-15 (10.3%)	High >15 (0.5%)	
Smoking	4.7	9.2	9.3	<0.001
Previous AMI	3.6	9.1	6.6	<0.001
Previous PCI	2.0	6.8	4.3	<0.001
Previous CABG	2.8	7.7	7.0	<0.001
Anaemias	1.4	20.2	37.9	<0.001
Valvular disease	0.5	4.8	7.0	<0.001
Peripheral vascular disease	0.2	2.4	4.5	<0.001
Coagulopathy	0.3	9.0	17.7	<0.001
Diabetes Mellitus	18.3	39.0	40.7	<0.001
Liver disease	0.6	11.5	20.0	<0.001
Chronic renal failure	6.1	32.4	44.1	<0.001
Chronic pulmonary disease	8.3	22.1	24.7	<0.001
Length of stay (days), median (IQR)	1 (0, 1)	2 (1, 5)	4 (2, 11)	<0.001
Total ED and in-hospital charges (USD), median (IQR)	25,990 (15,202, 46,584)	51,916 (27,889, 99,687)	88,357 (46,312, 176,094)	<0.001

Abbreviations: AMI – Acute Myocardial Infarction; CABG – Coronary Artery Bypass Graft; ED – Emergency Department; IQR – Interquartile Range; PCI – Percutaneous Coronary Intervention; USD – United States Dollar.

There were 458,987 encounters for acute haemorrhagic stroke. 214,968 (46.9%) had a high HFRS, 195,128 (42.6%) had an intermediate HFRS and 48,488 (10.6%) had a low HFRS. Patients admitted for acute haemorrhagic stroke with a high HFRS were likely to be as old as patients with an intermediate HFRS and older than those with a low HFRS (median age 71 for high HFRS vs 71 for intermediate HFRS and 67 for low HFRS). Patients with a high HFRS were more likely to be female (48.3% for high HFRS vs 47.8% for intermediate HFRS and 46.4% for low HFRS) and less comorbid with conditions such as anaemias (24.5% for high HFRS vs 15.6% for intermediate HFRS and 3.6% for low HFRS), diabetes (31.0% for high

HFRS vs 28.2% for intermediate HFRS and 17.1% for low HFRS), chronic pulmonary disease (12.7% for high HFRS vs 11.2% for intermediate HFRS and 4.9% for low HFRS), and liver disease (3.0% for high HFRS vs 2.9% for intermediate HFRS and 1.0% for low HFRS) compared to patients with a low HFRS (all p<0.001) **(**

Table 4.11**)**.

Table 4.11 Characteristics of patients presenting with acute haemorrhagic stroke.

Characteristics	Hospital Frailty Risk Score			*p*-value
	Low <5 (46.9%)	**Intermediate 5-15 (42.6%)**	**High >15 (10.6%)**	
Number of weighted discharges	214,968	195,128	48,488	
Age (years), median (IQR)	67 (55, 78)	71 (58, 81)	71 (58, 81)	<0.001
Female sex, %	47.9	47.9	48.6	<0.001
Weekend admission, %	26.5	26.5	27.3	<0.001
Primary expected payer, %				<0.001
Medicare	53.0	63.3	62.2	
Medicaid	10.5	10.7	14.0	
Private Insurance	25.7	18.9	17.1	
Self-pay	7.7	4.6	4.4	
No charge	0.3	0.3	0.3	
Other	2.8	2.2	2.0	
Median Household Income (percentile), %				<0.001
0-25th	29.1	29.9	30.4	
26th–50th	27.7	25.2	24.3	
51st-75th	23.1	23.2	23.1	
76th–100th	20.2	21.8	22.2	
Homelessness, %	0.2	0.4	0.3	<0.001
Comorbidities, %				

Characteristics	Hospital Frailty Risk Score			*p*-value
	Low <5 (46.9%)	Intermediate 5-15 (42.6%)	High >15 (10.6%)	
Dyslipidaemia	19.9	39.2	41.3	<0.001
Thrombocytopenia	2.0	6.3	8.2	<0.001
Smoking	9.2	10.4	10.6	<0.001
Previous AMI	2.8	5.6	4.7	<0.001
Previous PCI	2.5	5.7	4.0	<0.001
Previous CABG	2.5	5.2	4.1	<0.001
Anaemias	3.6	15.6	24.5	<0.001
Valvular disease	1.0	3.6	4.6	<0.001
Peripheral vascular disease	0.3	1.2	1.7	<0.001
Coagulopathy	3.6	11.0	14.2	<0.001
Diabetes Mellitus	17.1	28.2	31.0	<0.001
Liver disease	1.0	2.9	3.0	<0.001
Chronic renal failure	4.0	16.6	25.4	<0.001
Chronic pulmonary disease	4.9	11.2	12.7	<0.001
Length of stay (days), median (IQR)	3 (2, 6)	5 (2, 9)	10 (5, 19)	<0.001
Total ED and in-hospital charges (USD), median (IQR)	43,951 (23,126, 88,058)	62,802 (31,224, 138,057)	122,631 (57,268, 272,340)	<0.001

Abbreviations: AMI – Acute Myocardial Infarction; CABG – Coronary Artery Bypass Graft; ED – Emergency Department; IQR – Interquartile Range; PCI – Percutaneous Coronary Intervention; USD – United States Dollar.

There were 11,773,600 encounters for the 'Other CVD' group. 8,290,854 (70.4%) had a high HFRS, 3,304,205 (28.1%) had an intermediate HFRS and 178,541 (1.5%) had a low HFRS. Patients admitted with 'Other CVD' with a high HFRS were more likely to be older than those with an intermediate and low HFRS (median age 79 vs 72 for intermediate HFRS and 66 for low HFRS). Patients with a high HFRS were more likely to be female (56.4% vs 49.2% for intermediate HFRS and 50.7% for low HFRS) and more comorbid with conditions such as

anaemias (6.6% vs 36.1% for intermediate HFRS and 44.1% for low HFRS), thrombocytopaenia (8.3% vs 5.9% for intermediate HFRS and 1.1% for low HFRS), chronic pulmonary disease (29.0% for high HFRS vs 28.6% for intermediate HFRS and 9.0% for low HFRS), and chronic renal failure (62.7% for high HFRS vs 54.7% for intermediate HFRS and 11.2% for low HFRS) compared to patients with a low HFRS (all p<0.001) **(**

Table 4.12**)**.

Table 4.12 Characteristics of patients presenting with other cardiovascular diseases.

Characteristics	**Hospital Frailty Risk Score**			**p-value**
	Low <5 (70.4%)	**Intermediate 5-15 (28.1%)**	**High >15 (1.5%)**	
Number of weighted discharges	8,290,854	3,304,205	178,541	
Age (years), median (IQR)	66 (54, 77)	72 (61, 82)	79 (69, 86)	<0.001
Female sex, %	50.7	49.2	56.4	<0.001
Weekend admission, %	23.7	24.0	24.8	<0.001
Primary expected payer, %				<0.001
Medicare	45.2	72.5	83.3	
Medicaid	15.0	10.5	6.5	
Private Insurance	27.1	11.8	7.4	
Self-pay	9.4	3.2	1.4	
No charge	0.5	0.2	0.1	
Other	2.8	1.8	1.3	
Median Household Income (percentile), %				<0.001
0-25th	35.2	34.4	30.7	
26th–50th	27.3	26.1	24.9	
51st-75th	20.9	21.4	22.9	
76th–100th	16.6	18.1	21.4	
Comorbidities, %				
Dyslipidaemia	26.0	53.5	54.2	<0.001

Characteristics	Hospital Frailty Risk Score			p-value
	Low <5 (70.4%)	Intermediate 5-15 (28.1%)	High >15 (1.5%)	
Thrombocytopenia	1.1	5.9	8.3	<0.001
Smoking	12.2	10.9	6.7	<0.001
Previous AMI	6.8	14.4	11.9	<0.001
Previous PCI	6.8	13.4	9.2	<0.001
Previous CABG	5.0	12.4	9.4	<0.001
Anaemias	6.6	36.1	44.1	<0.001
Valvular disease	4.5	17.5	20.3	<0.001
Peripheral vascular disease	1.4	6.2	7.9	<0.001
Coagulopathy	1.7	7.7	10.7	<0.001
Diabetes Mellitus	22.0	46.7	45.2	<0.001
Liver disease	1.2	4.3	4.3	<0.001
Chronic renal failure	11.2	54.7	62.7	<0.001
Chronic pulmonary disease	9.0	28.6	29.0	<0.001
Length of stay (days), median (IQR)	2 (2, 4)	4 (2, 7)	7 (4, 12)	<0.001
Total charges (USD), median (IQR)	30,211 (17,007, 56,165)	36,900 (20,962, 69,341)	53,864 (29,065, 105,405)	<0.001

Abbreviations: AMI – Acute Myocardial Infarction; CABG – Coronary Artery Bypass Graft; ED – Emergency Department; IQR – Interquartile Range; PCI – Percutaneous Coronary Intervention; USD – United States Dollar.

4.2.3.6 Additional analyses

With the HFRS modelled as a continuous variable, increasing HFRS was associated with increased odds of home discharge, hospitalisation and ED mortality for all CVD admission groups. Interestingly, increasing HFRS was associated with increased odds of overall mortality for most CVD admission groups apart from cardiac arrest **(Table** 4.13**)**.

Table 4.13 Adjusted odds ratios of hospitalisation and ED mortality for selected ED cardiovascular admission diagnoses per 1-unit increase of HFRS*.

Admission Diagnosis	Hospital Frailty Risk Score

		aOR [95%CI]	*p*-value
Acute myocardial infarction (N =1,796,127)	**Hospitalisation**	1.34 [1.34-1.35]	<0.001
	ED mortality	0.85 [0.84-0.86]	<0.001
	Overall mortality	1.15 [1.15-1.16]	<0.001
Ischaemic stroke (N =1,662,442)	**Hospitalisation**	1.31 [1.30-1.31]	<0.001
	ED mortality	0.87 [0.85-0.88]	<0.001
	Overall mortality	1.12 [1.12-1.13]	<0.001
Atrial fibrillation/flutter (N =2,056,294)	**Hospitalisation**	1.35 [1.34-1.35]	<0.001
	ED mortality	1.03 [1.01-1.05]	<0.001
	Overall mortality	1.24 [1.23-1.25]	<0.001
Heart failure (N =1,483,837)	**Hospitalisation**	1.53 [1.52-1.53]	<0.001
	ED mortality	0.95 [0.93-0.96]	<0.001
	Overall mortality	1.21 [1.21-1.22]	<0.001
Pulmonary Embolism (N=627,547)	**Hospitalisation**	1.38 [1.37-1.39]	<0.001
	ED mortality	0.86 [0.84-0.88]	<0.001
	Overall mortality	1.20 [1.20-1.22]	<0.001
Cardiac arrest (N=495,406)	**Hospitalisation**	1.75 [1.74-1.76]	<0.001
	ED mortality	0.71 [0.70-0.72]	<0.001
	Overall mortality	0.88 [0.87-0.89]	<0.001
Haemorrhagic stroke (N =458,987)	**Hospitalisation**	1.39 [1.38-1.39]	<0.001
	ED mortality	0.84 [0.83-0.85]	<0.001
	Overall mortality	1.05 [1.04-1.05]	<0.001
Other CVD (N=11,773,600)	**Hospitalisation**	1.40 [1.39-1.40]	<0.001
	ED mortality	0.93 [0.92-0.93]	<0.001
	Overall mortality	1.19 [1.18-1.19]	<0.001

*1-unit increase in the HFRS.

Multivariable logistic regression model adjusted for: age, sex, weekend admission, primary expected payer, median household income, region and teaching status of the hospital, dyslipidaemia, smoking, thrombocytopenia, previous AMI, anaemia, coagulopathies, liver disease, diabetes, malignancy, peripheral vascular disease, chronic pulmonary disease, chronic renal disease and valvular heart diseases.

Abbreviations: aOR – adjusted Odds Ratio; CI – Confidence Interval; ED – Emergency Department; HFRS – Hospital Frailty Risk Score.

4.2.4 Discussion

4.2.4.1 Main findings

This study was a national analysis of the prevalence, clinical characteristics, phenotypes, and clinical outcomes of patients admitted to ED with CVD stratified by the HFRS. There are several important findings. Firstly, frailty is present in a significant proportion of CVD patients encounters in the ED. Secondly, there were important frailty-based differences in the clinical characteristics between HFRS groups, with high HFRS patients generally being older, female

and more comorbid. Thirdly, high HFRS was associated with a higher crude rates of hospitalisation and lower crude rates of home discharge compared to low HFRS. Finally, higher HFRS is associated with decreased ED mortality but increased overall mortality among most CVD phenotypes.

4.2.4.2 Prevalence of frailty

As demonstrated in Chapter 1, few studies use the HFRS, and of these, few involve specific CVD cohorts. Most CVD studies using the HFRS focusing on HF or ACS [89, 90, 95, 103]. One study used the HFRS in the ED cohort of 12,237 patients [159]. Interestingly, around 17.5% of these patients had a high HFRS, with the most having an intermediate (47.9%) and low HFRS (34.5%). However, the study did not investigate CVD specific encounters but rather evaluated all encounters, and only included patients aged over 75 [159]. The observed different distribution of HFRS in our study may reflect that the ED population admitted for CVD is less frail when not restricted by age, given frailty risk increases with age. Studies using measures such as the FI or FP estimated the prevalence of frailty to be between 1% to 91%. In studies using CVD-specific cohorts, the prevalence is estimated it to be between 15% and 41% [16, 78]. As discussed in Chapter 1, the wide range in reported prevalence may be due to the heterogeneity between frailty measures, with variations in what each score captures. In addition, there is further heterogeneity in the populations included in these studies [160]. Frailty was associated with specific clinical characteristics such as increasing age, female sex and comorbidities, in line with previous literature [82]. Interestingly, high HFRS was associated with lower prevalence of previous AMI, previous PCI and previous CABG compared to the intermediate HFRS group. This could be due survivorship bias, as patients with severe CVD are less likely to live longer, whereas frailty increases with age [161].

4.2.4.3 Frailty and cardiovascular disease encounters

In this analysis, there were variations in frailty status across most CVD admissions. AF was a rare cause of admission in the high HFRS group but interestingly was associated with the worst prognosis. Although the associated wide 95%CI, possibly demonstrating a degree of imprecision, should be considered. Poor outcomes in AF patients could be explained by AF having several clinical associations. It is associated with increasing age, comorbidity burden and stroke risk [58, 162, 163]. Frailty predisposes to AF through changes in left atrial volume in the ageing heart [162]. Furthermore, AF patients are more likely to receive treatment with an anticoagulant to decrease the risk of stroke, and therefore this could have mediated outcomes in lower risk patients [164]. However, frailty can be described as a relative contraindication to anticoagulation, particularly for patients with a high bleeding risk, meaning highly frail patients are less likely to be anticoagulated, leading to the occurrence of thrombotic complications [165]. Acute ischaemic stroke was the most common cause of admission in the intermediate HFRS group. The acute ischaemic stroke cohort had the highest proportion of patients with a high HFRS and was also associated with the worst prognosis of all CVD admissions in the high HFRS group. Acute ischaemic stroke is considered a condition of older age like AF, with 70% of strokes occurring after the age of 65 [55]. There are no studies describing the prevalence of PE, cardiac arrest, and acute haemorrhagic stroke stratified by the presence of frailty.

Cardiac arrest and haemorrhagic stroke had high proportions of patients at low or intermediate risk of frailty. This could also be due to a couple of reasons. Firstly, this could be due to the inherent poor prognosis of these conditions, independent of frailty status [68, 69, 72]. Secondly, this could be due to potential selection bias with only the most robust patients that are frail surviving to hospital admission.

HF admissions had a high proportion of intermediate or high HFRS patients. No studies have used the HFRS to study HF in the ED setting. In hospital studies, the reported prevalence of intermediate and high HFRS in HF varies [90, 102]. A HF study of an US cohort estimated the prevalence of intermediate and high HFRS to be 19.9% and 0.1% respectively. An Australian study reported a similar distribution [91], and contrasts with another hospital study of Medicare beneficiaries who reported a prevalence of 47.4% and 25.0% for intermediate and high HFRS respectively [90, 102]. This further demonstrates that this ED cohort represents a clinically different group to those observed in hospital studies using the HFRS.

In this analysis, increased HFRS was associated with decreased crude rates of ED mortality and increased crude rates of in-hospital mortality. This could be due to early identification and triaging of patients with higher frailty risk, leading to a lower likelihood of adverse outcomes in the ED setting, but overall worse prognosis during their in-hospital stays. Although it is hard to delineate the exact mechanisms underlying the present findings, it should be noted that frail patients were less likely to be discharged home and more likely to be hospitalised and have higher in-hospital mortality. There have been no studies evaluating the difference in ED and hospital mortality in ED patients, and whether highly frail patients are more likely to be triaged sooner. Studies investigating frailty in the ED generally focus on in-hospital mortality or 30-day mortality [166-168]. Few studies have utilised the HFRS [94, 159].

As mentioned previously, many cases of cardiac arrest occur out-of-hospital, and those that make it into the hospital or occur in the hospital have very poor outcomes [68, 69]. This was reflected in our analysis where cardiac arrest patients had the highest rates of ED mortality across all HFRS groups. For most other CVD admissions in our analysis, patients survived ED admission but suffered poor outcomes in-hospital.

4.2.4.4 Clinical implications

There are several important clinical implications of this study. Firstly, this study reaffirms frailty represents a significant proportion of patients seen in ED, with over half of patients at high risk. This outlines the importance of a frailty assessment in the ED, adding to the growing body of research into frailty assessments in the ED [169-171]. It is important to identify patients at risk of frailty, for appropriate management to prevent adverse complications and improve quality of life [172]. Moreover, frailty can be reversed, exemplifying the need for early identification and optimisation of risk factors [173]. Secondly, coexistence of frailty and comorbidity among patients with CVD represent a challenge for healthcare services through increased length of stay, total costs and mortality. Knowledge of the trends and outcomes of CVD in frail patients is important to deliver improved care or this at-risk group. Finally, this study prompts the early recognition and management of CVD and frailty in the community, which could have an impact on acute and unplanned admissions [174].

4.2.4.5 Limitations

This study includes several limitations inherent to the NEDS database. Firstly, coded databases are susceptible to selection bias due to missing data, miscoding, and misdiagnosis. Secondly, given this is an observational study, confounding bias could not be eliminated despite the broad range of conditions covered by the NEDS. Thirdly, useful clinical information that could provide a more granular analysis such as race and pharmacological management of patients are not available using the NEDS. Finally, detailed analysis of longitudinal outcomes could not be assessed as the NEDS only captures ED and in-hospital outcomes only.

4.2.5 Conclusions

ED encounters for CVD vary by frailty status with ischaemic stroke being the most common cause in high-risk patients, followed by haemorrhagic stroke and AMI, and cardiac arrest is the most common encounter in low-risk patients, followed by AF and AMI. Patient encounters for CVD in the ED have high frailty burden, which is associated with a worse prognosis, including the highest overall mortality in patients with high HFRS, across most CVD phenotypes. Future studies are needed to define the long term relationship between frailty and mortality in this setting.

4.3 Hospital admissions

4.3.1 Introduction

The first chapter of this thesis established that there is a paucity of literature using the HFRS in patients with CVD. Studies using the HFRS varied in there reporting and granularity. Whilst there are many studies utilising frailty measures for specific CVD, there is little data investigating whether CVD admissions vary by frailty status and whether frailty is associated with in-hospital outcomes in patients admitted with acute CVD conditions. One study used the HFRS in an overall CVD cohort, where 5 conditions were specifically investigated due to their overall prevalence: AF, chronic IHD, HF, hypotension and primary hypertension [101]. Overall, the increasing HFRS is associated with higher prevalence of female sex, non-white race, comorbidities and increased likelihood of adverse outcomes such as hospital length of stay, readmission and all-cause mortality.

The first part of the results of this thesis referred to the study that evaluated the HFRS in CVD specific encounters in the ED. Broadly, the HFRS in the ED setting positively predicted adverse

outcomes. However, the complete understanding of the association between CVD and frailty cannot be investigated solely with the ED data. Analyses of in-hospital period are beneficial to provide a broader representation of the relationship between CVD and frailty. This allows for an analysis of the causes and outcomes of frail patients admitted to hospital with CVD. Information on the causes of CVD admissions and their associated outcomes would be fundamental in planning healthcare services around the growing frail population.

Therefore, the aim of this study was to describe the prevalence, clinical characteristics, and in-hospital mortality of patients with the CVD admissions of interest based on their frailty status, as measured by the HFRS. The findings from this study have been published in the American Journal of Cardiology **(Appendix 13)** [175].

4.3.2 Methods

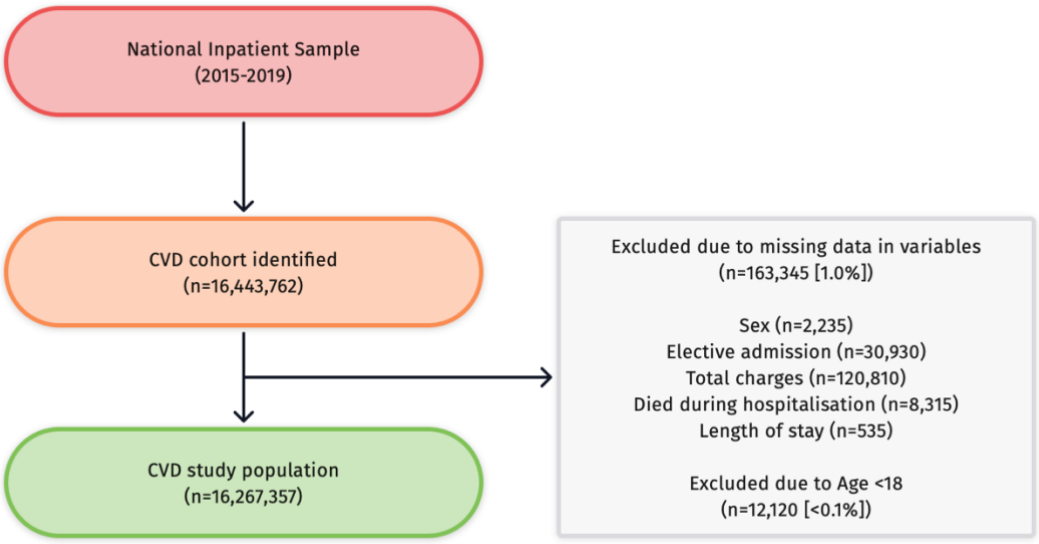
The general methods of this study were described in Chapter 3. Briefly, the NIS database of hospitalisations across the US was used for this study. The NIS is the largest available database of US hospitalisations developed for the HCUP sponsored by the AHRQ, containing anonymised data on diagnoses and procedures from over 7 million hospitalisations annually, representing a 20% stratified sample of all discharges from US community hospitals, excluding rehabilitation and long-term acute care hospitals [142]. An overview of the NIS was provided in Chapter 3.

The HFRS was used to stratify all patients by frailty risk. The HFRS was developed by Gilbert et al. to establish whether elderly patients at risk of adverse outcomes could be identified using routinely collected healthcare data [10]. An overview of its development was provided in Chapter 1. The pivotal study analysed cohort of patients aged 75 and over that were hospitalised with diagnoses associated with frailty [10]. The HFRS was then created by grouping the

identified patients according to their ICD-10-CM codes into 3 groups: low risk (HFRS <5), intermediate risk (HFRS 5-15) and high risk (HFRS >15) [10].

ICD-10-CM codes were used to identify all adult hospitalisations with a principal discharge diagnosis of CVD between October 2015 and December 2019. This sample was further filtered by focusing on the 7 CVD admissions of interest as outlined in Chapter 1: AMI, AF, acute ischaemic stroke, HF, PE, CA, and acute haemorrhagic stroke. Further stratification was done according to their frailty status by HFRS into the low, intermediate, and high risk of frailty. Cases with missing data for the following variables were excluded: age, sex, elective admission, in-hospital mortality, primary expected payer, total charges and length of stay. These cases accounted for no more than 1.0% of the original dataset (**Figure 4.6**). This observational study was appraised according to the *STROBE* recommendations [176].

Figure 4.6 Flow diagram of the cohort selection process.



Median and interquartile range (IQR) were used to summarise continuous variables such as age, length of stay and total charges. Chi-squared (X^2) test was used to compare categorical

variables and results were summarised as percentages (%). Multivariable logistic regression was performed to determine the adjusted odds ratio (aOR) of all-cause mortality. The logistic regression model was adjusted for the following variables: age, sex, race, weekend admission, primary expected payer, median household income, bed size of hospital, region of hospital, location/teaching status of hospital, smoking status, previous AMI, previous percutaneous coronary intervention (PCI), previous coronary artery bypass graft (CABG), dyslipidaemia, and Elixhauser comorbidities (anaemias, coagulopathy, diabetes mellitus, liver disease, metastatic cancer, PVD and chronic renal failure). aOR had 95% confidence intervals (CI) and results were determined significant at the level of $p<0.05$. All statistical analyses were weighted and performed using SPSS version 27 (IBM Corp, Armonk, NY) [155].

4.3.3 Results

4.3.3.1 Cohort characteristics

A total of 16,267,357 discharges with acute CVD admissions were identified, while a total of 9,307,398 discharges had one of the 7 cardiovascular diagnoses of interest (acute myocardial infarction, acute ischaemic stroke, atrial fibrillation, heart failure, pulmonary embolism, and acute haemorrhagic stroke)

Overall, 10,033,793 discharges (61.7%) had a HFRS of <5, 5,834,375 (35.9%) had a HFRS of 5-15 and 399,150 (2.5%) had a HFRS of >15. Patients with a HFRS >15 were more likely to be older (median age 75 for high HFRS vs. 72 for intermediate HFRS and 68 for low HFRS) and female (54.5% for high HFRS vs. 48.9% for intermediate HFRS and 42.4% for low HFRS) and have a higher prevalence of hypertension and coagulopathy, as well as a lower prevalence of smoking, previous AMI, previous PCI, previous CABG, heart failure and diabetes, compared to patients with a HFRS <5 and HFRS 5-15 (all $p<0.001$) **(Table** 4.14**)**.

Table 4.14 Patient characteristics for all cardiovascular admissions according to HFRS.

Characteristics	Hospital Frailty Risk Score			p-value
	Low <5 (61.7%)	Intermediate 5-15 (35.9%)	High >15 (2.4%)	
Number of weighted discharges	10,033,793	5,834,375	399,190	
Age (years), median (IQR)	68 (58,78)	72 (62,82)	75 (64,84)	<0.001
Female sex, %	42.4	48.9	54.5	<0.001
Ethnicity, %				<0.001
White	72.6	68.7	65.4	
Black	13.8	17.2	19.2	
Hispanic	8.1	8.4	8.7	
Other	5.5	5.7	6.7	
Weekend admission, %	20.6	23.3	25.0	<0.001
Primary expected payer, %				<0.001
Medicare	60.2	71.8	73.4	
Medicaid	10.0	9.1	9.3	
Private Insurance	23.1	14.2	12.7	
Self-pay	3.9	2.8	2.7	
No charge	0.3	0.2	0.2	
Other	2.5	2.0	1.7	
Median Household Income (percentile), %				<0.001
0-25th	30.4	31.4	30.9	
26th–50th	26.9	26.4	25.6	
51st-75th	23.8	23.7	23.9	
76th–100th	18.8	18.6	19.7	
Homelessness, %	0.6	0.5	0.4	<0.001
Comorbidities, %				
Atrial fibrillation	32.8	34.4	32.2	<0.001
Dyslipidaemia	55.8	55.4	54.5	<0.001
Thrombocytopenia	4.1	6.6	6.5	<0.001

Characteristics	Hospital Frailty Risk Score			p-value
	Low <5 (61.7%)	Intermediate 5-15 (35.9%)	High >15 (2.4%)	
Smoking	11.7	9.3	8.5	<0.001
Previous AMI	12.7	11.8	7.9	<0.001
Previous PCI	14.1	11.1	6.6	<0.001
Previous CABG	9.9	9.7	6.2	<0.001
Anaemias	15.5	29.2	26.5	<0.001
Congestive heart failure	44.9	52.6	33.7	<0.001
Valvular disease	6.1	6.0	3.8	<0.001
Hypertension	70.4	72.8	74.8	<0.001
Peripheral vascular disease	9.9	11.0	9.5	<0.001
Coagulopathy	5.4	8.9	9.6	<0.001
Diabetes Mellitus	24.1	21.3	19.1	<0.001
Liver disease	3.0	4.8	3.3	<0.001
Chronic renal failure	18.5	42.7	36.8	<0.001
Bed size of hospital, %				<0.001
Small	18.9	17.9	13.7	
Medium	29.5	28.7	27.0	
Large	52.7	51.4	60.3	
Hospital Region, %				<0.001
Northeast	19.4	17.5	15.0	
Midwest	21.6	23.1	26.0	
South	41.7	41.1	40.4	
West	17.0	18.3	18.6	
Location/teaching status of hospital, %				<0.001
Rural	8.7	7.7	4.8	
Urban non-teaching	22.2	20.3	15.6	
Urban teaching	69.1	72.1	79.6	
Length of stay, median (IQR)	3 (2, 4)	5 (3,8)	8 (4,14)	<0.001

Characteristics	Hospital Frailty Risk Score			p-value
	Low <5 (61.7%)	Intermediate 5-15 (35.9%)	High >15 (2.4%)	
Total charges, median (IQR)	39,312 (20,083, 79,673)	47,413 (25,787, 96,500)	78,330 (40,791, 162,103)	<0.001
All-cause in-hospital mortality, %	1.5	6.0	9.6	<0.001

Abbreviations: AMI – Acute Myocardial Infarction; CABG – Coronary Artery Bypass Graft; IQR – Interquartile Range; PCI – Percutaneous Coronary Intervention; USD – United States Dollar.

4.3.3.2 Cause of admission

The most common cause of CVD admission in the low HFRS group was 'Other CVD', followed by AMI and acute ischaemic stroke. Acute ischaemic stroke was the most common CVD admission for the intermediate and high HFRS groups, followed by 'Other CVD' and AMI for the intermediate HFRS, and followed by 'Other CVD' and acute haemorrhagic stroke for the high HFRS of >15 group **(Table** 4.15 and **Figure 4.5)**.

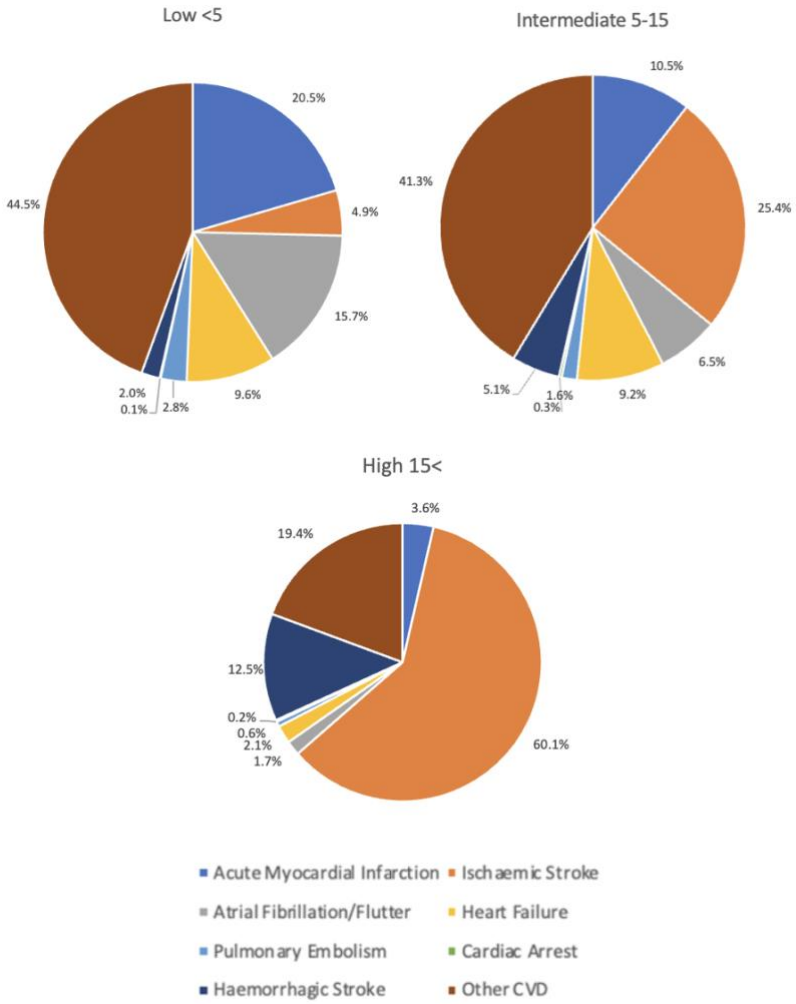
Table 4.15 Prevalence of the cardiovascular admission diagnoses within each HFRS category and associated mortality within each CVD admission group.

Admission diagnosis		Hospital Frailty Risk Score			p-value
		Low <5 (61.7%)	Intermediate 5-15 (35.9%)	High >15 (2.4%)	
Acute myocardial infarction (N =2,677,890)	**Prevalence**	20.5	10.5	3.5	<0.001
	In-hospital mortality	2.2	12.7	15.4	<0.001
Acute ischaemic stroke (N =2,217,925)	**Prevalence**	4.9	25.4	60.1	<0.001
	In-hospital mortality	2.0	3.8	8.9	<0.001
Atrial fibrillation/flutter (N =1,959,699)	**Prevalence**	15.7	6.5	1.7	<0.001
	In-hospital mortality	0.3	2.9	8.0	<0.001
	Prevalence	9.6	9.2	2.1	<0.001

Admission diagnosis		Hospital Frailty Risk Score			p-value
		Low <5 (61.7%)	Intermediate 5-15 (35.9%)	High >15 (2.4%)	
Heart failure (N =1,511,459)	**In-hospital mortality**	1.7	5.4	12.3	<0.001
Pulmonary Embolism (N=375,940)	**Prevalence**	2.8	1.6	0.6	<0.001
	In-hospital mortality	1.4	8.5	10.6	<0.001
Cardiac arrest (N=28,790)	**Prevalence**	0.1	0.3	0.2	<0.001
	In-hospital mortality	71.7	74.0	55.2	<0.001
Acute haemorrhagic stroke (*N* =545,695)	**Prevalence**	2.0	5.1	12.5	<0.001
	In-hospital mortality	17.8	20.7	15.0	<0.001
Other CVD (N=6,949,960)	**Prevalence**	44.5	41.3	19.4	<0.001
	In-hospital mortality	0.7	3.7	6.5	<0.001

Abbreviations: CVD – Cardiovascular disease.

Figure 4.7 Distribution of selected cardiovascular admission causes within each HFRS category.



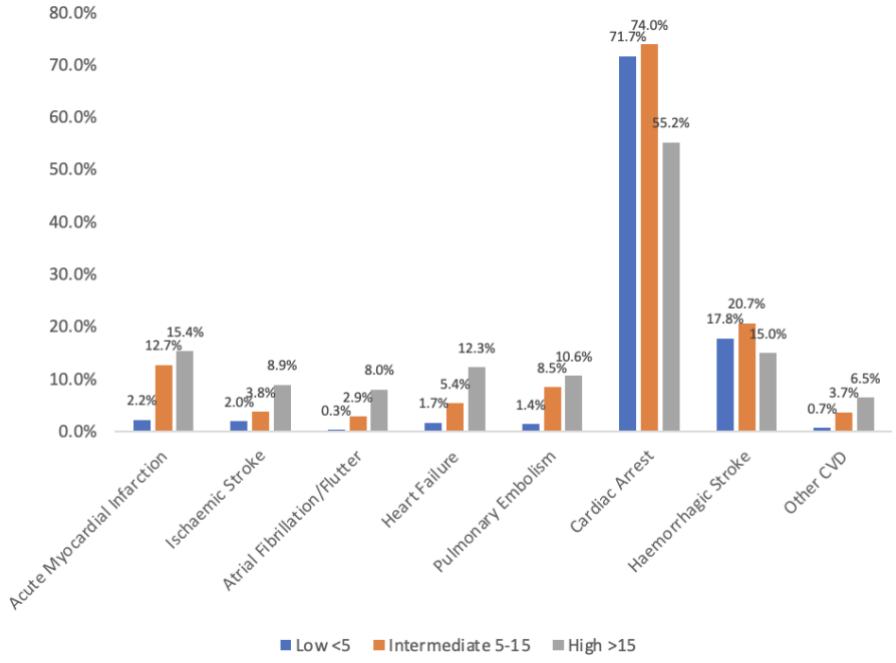
Abbreviations: CVD – Cardiovascular disease.

4.3.3.3 Mortality

Patients with HFRS of >15 had higher unadjusted rates of all-cause mortality compared to their lower frailty counterparts (9.6% for high HFRS vs 6.0 for intermediate HFRS and 1.5% for low HFRS). Increased unadjusted rates of all-cause mortality for high risk frailty patients was also observed in patients admitted with AMI (15.4% for high HFRS vs 12.7% for intermediate HFRS and 2.2% for low HFRS), acute ischaemic stroke (8.9% for high HFRS vs 3.8% for intermediate HFRS and 2.0% for low HFRS), AF (8.0% for high HFRS vs 2.9% for intermediate HFRS and 0.3% for low HFRS), HF (12.3% for high HFRS vs 5.4% for intermediate HFRS and 1.7% for low HFRS) and PE (10.6% for high HFRS vs 8.5% for

intermediate HFRS and 1.4% for low HFRS), but not for patients admitted with cardiac arrest (55.2% for high HFRS vs 74.0% for intermediate HFRS group and 71.3% for low HFRS) or acute haemorrhagic stroke (15.0% for high HFRS vs 20.7% for intermediate HFRS and 17.8% for low HFRS) **(Figure** 4.8**).**

Figure 4.8. In-hospital mortality in different frailty risk categories and cardiovascular admission diagnoses.



Abbreviations: CVD – Cardiovascular disease.

After adjustment for baseline characteristics, increasing frailty risk was associated with increased odds of all-cause mortality. Patients with an intermediate or high HFRS admitted for AF had the highest odds of all-cause mortality (aOR 17.69, 95% CI 16.08 to 19.45 for high HFRS group, aOR 6.75, 95% CI 6.51 to 7.00 for intermediate HFRS group). Increased odds of mortality were also observed for patients admitted with AMI, acute ischaemic stroke, HF, PE, and other CVD admission diagnoses ($p<0.001$). Interestingly, a decreased odds of mortality in the high HFRS group was observed in patients admitted for cardiac arrest and acute haemorrhagic stroke only (aOR 0.46, 95% CI 0.39 to 0.55 for cardiac arrest patients with a

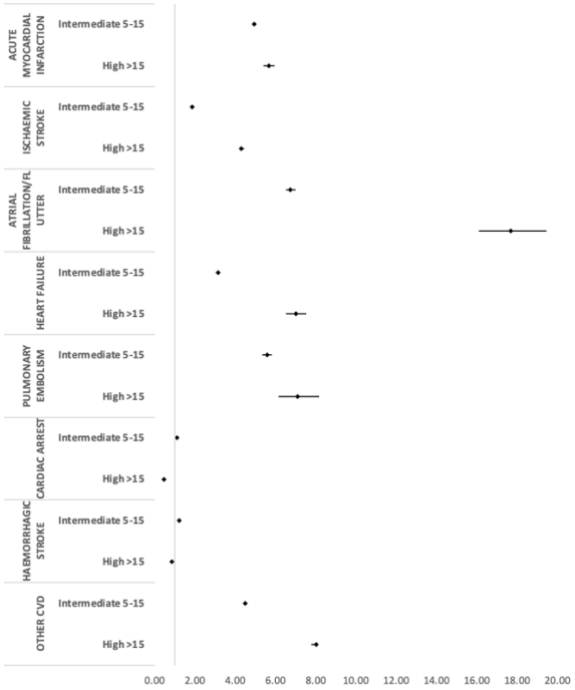
high HFRS, aOR 0.86, 95% CI 0.83 to 0.88 for acute haemorrhagic stroke patients with a high HFRS) **(Table** 4.16 and **Figure** 4.9**)**.

Table 4.16. Adjusted odds ratios of mortality in different HFRS categories and selected cardiovascular admission diagnoses*.

Admission Diagnosis	Hospital Frailty Risk Score			
	Intermediate 5-15 (35.9%)		High >15 (2.4%)	
	aOR [95%CI]	p-value	aOR [95%CI]	p-value
Acute myocardial infarction (N =2,677,890)	4.95 [4.86-5.02]	<0.001	5.67 [5.39-5.96]	<0.001
Acute ischaemic stroke (N =2,217,925)	1.88 [1.84-1.92]	<0.001	4.31 [4.20-4.43]	<0.001
Atrial fibrillation/flutter (N =1,959,699)	6.75 [6.51-7.00]	<0.001	17.69 [16.08-19.45]	<0.001
Heart failure (N =1,511,459)	3.15 [3.08-3.22]	<0.001	7.01 [6.52-7.53]	<0.001
Pulmonary Embolism (N=375,940)	5.58 [5.34-5.82]	<0.001	7.09 [6.14-8.18]	<0.001
Cardiac arrest (N=28,790)	1.12 [1.05-1.20]	<0.001	0.46 [0.39-0.55]	<0.001
Acute haemorrhagic stroke (N=545,695)	1.21 [1.20-1.23]	<0.001	0.86 [0.83-0.88]	<0.001
Other CVD (N=6,949,960)	4.49 [4.43-4.54]	<0.001	8.02 [7.77-8.29]	<0.001

*Reference group is low HFRS score <5 for each CVD admission diagnosis.
Multivariable logistic regression model adjusted for: age, sex, race, weekend admission, elective admission, primary expected payer, median household income, hospital bed size, region and teaching status, thrombocytopenia, previous PCI, previous AMI, previous CABG, anaemia, coagulopathies, liver disease, metastatic disease, PVD.
Abbreviations: aOR – Adjusted odds ratio; CI – Confidence interval; CVD – Cardiovascular disease.

Figure 4.9 Adjusted mortality rates for different frailty risk category and selected cardiovascular admission causes*.



*Reference group is low HFRS score <5 for each CVD admission diagnosis.

Multivariable logistic regression model adjusted for: age, sex, race, weekend admission, elective admission, primary expected payer, median household income, hospital bed size, region and teaching status, thrombocytopenia, previous PCI, previous AMI, previous CABG, anaemia, coagulopathies, liver disease, metastatic disease, PVD.

Abbreviations: CVD – Cardiovascular disease.

4.3.3.4 Subgroup analyses

A total of 2,677,890 patients were admitted with AMI. 13,805 (0.5%) had a high HFRS, 610,185 (22.8%) had an intermediate HFRS and 2,053,900 (76.6%) had a low. Patients admitted for AMI with a HFRS of >15 were more likely to be older (median age 77 for high HFRS vs 73 for intermediate HFRS and 65 for low HFRS) and female (51.7% for high HFRS vs 44.0% for intermediate HFRS and 35.4% for low HFRS) and less likely to be white (69.5% for high HFRS vs 71.7% for intermediate HFRS and 74.5% for low HFRS). High risk patients with AMI were more comorbid with conditions such as AF (30.9% for high HFRS vs 27.9% for intermediate HFRS and 14.5% for low HFRS), anaemia (42.6% for high HFRS vs 36.8% for intermediate HFRS and 12.5% for low HFRS), HF (68.9% for high HFRS vs 64.1% for intermediate HFRS and 34.4% for low HFRS), chronic renal failure (56.8% for high HFRS vs

50.4% for intermediate HFRS and 14.1% for low HFRS) and coagulopathy (14.4% for high HFRS vs 12.0% for intermediate HFRS and 4.3% for low HFRS) compared to patients with an intermediate or low HFRS (all p<0.001) **(Table** 4.17**).**

Table 4.17 Characteristics of patients admitted with acute myocardial infarction.

Characteristics	Hospital Frailty Risk Score			p-value
	Low <5 (76.7%)	Intermediate 5-15 (22.8%)	High >15 (0.5%)	
Number of weighted discharges	2,053,900	610,185	13,805	
Age (years), median (IQR)	65 (56, 75)	73 (64, 82)	77 (68, 84)	<0.001
Female sex, %	35.4	44.0	51.7	<0.001
Ethnicity, %				<0.001
White	74.5	71.7	69.5	
Black	10.7	12.5	13.4	
Hispanic	8.5	9.1	9.4	
Other	6.3	6.7	7.7	
Weekend admission, %	26.4	26.4	26.3	<0.001
Primary expected payer, %				<0.001
Medicare	51.8	74.0	79.3	
Medicaid	9.9	7.7	6.6	
Private Insurance	29.4	13.5	10.2	
Self-pay	5.4	2.5	1.7	
No charge	0.5	0.2	0.2	
Other	3.0	2.2	2.1	
Median Household Income (percentile), %				<0.001
0-25th	30.3	31.7	31.7	
26th–50th	27.5	27.2	25.8	
51st-75th	23.8	23.3	23.5	
76th–100th	18.4	17.8	19.0	
Homelessness, %	0.3	0.4	0.3	<0.001

Characteristics	Hospital Frailty Risk Score			p-value
	Low <5 (76.7%)	Intermediate 5-15 (22.8%)	High >15 (0.5%)	
Comorbidities, %				
Atrial fibrillation	14.5	27.9	30.9	<0.001
Dyslipidaemia	64.9	61.8	58.5	<0.001
Thrombocytopenia	3.5	9.3	11.1	<0.001
Smoking	13.9	7.8	5.1	<0.001
Previous AMI	14.7	16.7	13.7	<0.001
Previous PCI	16.6	16.5	12.0	<0.001
Previous CABG	9.2	11.6	9.0	<0.001
Anaemias	12.5	36.8	42.6	<0.001
Congestive heart failure	34.4	64.1	68.9	<0.001
Valvular disease	5.3	8.3	6.4	<0.001
Hypertension	66.2	56.9	58.3	<0.001
Peripheral vascular disease	7.7	13.0	13.0	<0.001
Coagulopathy	4.3	12.0	14.4	<0.001
Diabetes Mellitus	28.1	30.1	24.7	<0.001
Liver disease	2.0	5.9	6.7	<0.001
Chronic renal failure	14.1	50.4	56.8	<0.001
Length of stay (days), median (IQR)	2 (2,4)	5 (3,10)	10 (5,17)	<0.001
Total charges (USD), median (IQR)	63,869 (36,566, 104,660)	84,998 (40,434, 172,640)	123,014 (54,836, 259,834)	<0.001

Abbreviations: AMI – Acute Myocardial Infarction; CABG – Coronary Artery Bypass Graft; IQR – Interquartile Range; PCI – Percutaneous Coronary Intervention; USD – United States Dollar.

A total of 2,217,925 were admitted for acute ischaemic stroke. 239,720 (10.8%) had a high HFRS, 1,482,910 (66.9%) had an intermediate HFRS and 495,295 (22.3%) had a low HFRS. Patients admitted for acute ischaemic stroke with a high HFRS were more likely to be older (median age 76 for high HFRS vs 72 for intermediate HFRS and 69 for low HFRS) and female (54.8% for high HFRS vs 50.1% for intermediate HFRS and 47.0% for low HFRS) and less

likely to be white (66.2% for high HFRS vs 68.4% for intermediate HFRS and 70.4% for low HFRS). High HFRS patients with acute ischaemic stroke were more comorbid with conditions such as AF (31.6% for high HFRS vs 22.4% for intermediate HFRS and 16.9% for low HFRS), thrombocytopaenia (5.0% for high HFRS vs 3.0% for intermediate HFRS and 2.1% for low HFRS), anaemias (20.9% for high HFRS vs 11.9% for intermediate HFRS and 7.1% for low HFRS %), HF (26.4% for high HFRS vs 18.5% for intermediate HFRS and 13.3% for low HFRS), chronic renal failure (31.1% for high HFRS vs 17.7% for intermediate HFRS and 8.8% for low HFRS) and PVD (8.8% for high HFRS vs 7.5% for intermediate HFRS and 6.1% for low HFRS) compared to patients with an intermediate or low HFRS (p<0.001) (**Table** 4.18**).**

Table 4.18 Characteristics of patients admitted with acute ischaemic stroke.

Characteristics	**Hospital Frailty Risk Score**			**p-value**
	Low <5 (22.3%)	**Intermediate 5-15 (66.9%)**	**High >15 (10.8%)**	
Number of weighted discharges	495,295	1,482,910	239,720	
Age (years), median (IQR)	69 (59, 79)	72 (61, 82)	76 (65, 85)	<0.001
Female sex, %	47.0	50.1	54.8	<0.001
Ethnicity, %				<0.001
White	70.4	68.4	66.2	
Black	15.3	17.4	19.3	
Hispanic	8.5	8.1	8.1	
Other	5.8	6.1	6.4	
Weekend admission, %	24.5	26.1	26.5	<0.001
Primary expected payer, %				<0.001
Medicare	58.8	66.1	74.4	
Medicaid	9.1	9.2	8.8	
Private Insurance	24.6	18.1	12.1	
Self-pay	4.6	4.0	2.7	
No charge	0.4	0.3	0.2	

Characteristics	Hospital Frailty Risk Score			p-value
	Low <5 (22.3%)	Intermediate 5-15 (66.9%)	High >15 (10.8%)	
Other	2.5	2.2	1.8	
Median Household Income (percentile), %				<0.001
0-25th	29.6	31.2	31.2	
26th–50th	26.5	26.2	25.6	
51st-75th	24.3	23.8	23.7	
76th–100th	19.5	18.8	19.4	
Homelessness, %	0.2	0.3	0.4	<0.001
Comorbidities, %				<0.001
Atrial fibrillation	16.9	22.4	31.6	<0.001
Dyslipidaemia	54.8	57.9	58.0	<0.001
Thrombocytopenia	2.1	3.0	5.0	<0.001
Smoking	8.8	10.6	9.2	<0.001
Previous AMI	6.3	7.5	7.6	<0.001
Previous PCI	6.6	7.2	6.4	<0.001
Previous CABG	6.0	6.6	6.1	<0.001
Anaemias	7.1	11.9	20.9	<0.001
Congestive heart failure	13.3	18.5	26.4	<0.001
Valvular disease	3.9	3.9	3.7	<0.001
Hypertension	72.1	73.7	73.8	<0.001
Peripheral vascular disease	6.1	7.5	8.8	<0.001
Coagulopathy	3.7	4.9	7.6	<0.001
Diabetes Mellitus	30.0	27.6	22.0	<0.001
Liver disease	1.3	1.7	2.2	<0.001
Chronic renal failure	8.8	17.7	31.1	<0.001
Length of stay (days), median (IQR)	2 (2,4)	3 (2,6)	6 (4,11)	<0.001
Total charges (USD), median (IQR)	30,244 (19,213, 49,567)	40,663 (24,490, 71959)	68,798 (37,398, 134,111)	<0.001

Abbreviations: AMI – Acute Myocardial Infarction; CABG – Coronary Artery Bypass Graft; IQR – Interquartile Range; PCI – Percutaneous Coronary Intervention; USD – United States Dollar.

A total of 1,959,700 patients were admitted with AF. 6,970 (0.4%) had a high HFRS, 378,820 (19.3%) had an intermediate HFRS and 1,573,910 (80.3%) had a low HFRS. Patients admitted for AF with a high HFRS were more likely to be older (median age 81 for high HFRS vs 77 for intermediate HFRS and 71 for low HFRS) and female (65.5% for high HFRS vs 56.2% for intermediate HFRS and 47.5% for low HFRS) and less likely to be white (79.1% for high HFRS vs 80.5% for intermediate HFRS and 82.0% for low HFRS). High risk patients with AF were more comorbid with conditions such as thrombocytopaenia (8.5% for high HFRS vs 5.9% for intermediate HFRS and 2.7% for low HFRS), anaemias (33.9% for high HFRS vs 25.9% for intermediate HFRS and 10.0% for low HFRS), HF (58.5% for high HFRS vs 55.8% for intermediate HFRS and 40.1% for low HFRS), chronic renal failure (48.9% for high HFRS vs 40.1% for intermediate HFRS and 12.4% for low HFRS), coagulopathy (10.8% for high HFRS vs 7.9% for intermediate HFRS and 3.8% for low HFRS) and PVD (10.7% for high HFRS vs 8.9% for intermediate HFRS and 5.3% for low HFRS) compared to patients with an intermediate and low HFRS ($p<0.001$) **(**

Table 4.19**).**

Table 4.19 Characteristics of patients admitted with atrial fibrillation/flutter.

Characteristics	Hospital Frailty Risk Score			p-value
	Low <5 (80.3%)	Intermediate 5-15 (19.3%)	High >15 (0.4%)	
Number of weighted discharges	1,573,910	378,820	6,970	
Age (years), median (IQR)	71 (61, 79)	77 (68, 85)	81 (74, 87)	<0.001
Female sex, %	47.5	56.2	65.5	<0.001
Ethnicity, %				<0.001
White	82.0	80.5	79.1	
Black	8.0	10.2	10.3	
Hispanic	6.0	5.6	5.2	
Other	4.0	3.7	5.4	
Weekend admission, %	19.4	22.0	24.7	<0.001
Primary expected payer, %				<0.001
Medicare	65.4	81.5	88.5	
Medicaid	6.4	5.3	3.1	
Private Insurance	23.1	10.2	6.1	
Self-pay	2.7	1.4	0.9	
No charge	0.2	0.1	0.1	
Other	2.1	1.5	1.3	
Median Household Income (percentile), %				<0.001
0-25th	26.9	29.0	30.3	
26th–50th	27.0	27.2	26.2	
51st-75th	25.1	24.3	25.0	
76th–100th	21.0	19.4	18.5	
Homelessness, %	0.4	0.6	0.1	<0.001
Comorbidities, %				
Atrial fibrillation	88.3	88.7	89.4	<0.001
Dyslipidaemia	48.4	51.5	51.0	<0.001
Thrombocytopenia	2.7	5.9	8.5	<0.001
Smoking	6.2	5.1	3.7	<0.001
Previous AMI	7.9	10.0	7.0	<0.001

Characteristics	Hospital Frailty Risk Score			p-value
	Low <5 (80.3%)	Intermediate 5-15 (19.3%)	High >15 (0.4%)	
Previous PCI	9.4	9.9	7.9	<0.001
Previous CABG	7.2	7.9	5.5	<0.001
Anaemias	10.0	25.9	33.9	<0.001
Congestive heart failure	40.1	55.8	58.5	<0.001
Valvular disease	8.0	8.7	8.6	<0.001
Hypertension	64.4	61.2	61.4	<0.001
Peripheral vascular disease	5.3	8.9	10.7	<0.001
Coagulopathy	3.8	7.9	10.8	<0.001
Diabetes Mellitus	21.7	22.2	17.6	<0.001
Liver disease	2.5	4.9	5.4	<0.001
Chronic renal failure	12.4	40.1	48.9	<0.001
Length of stay (days), median (IQR)	2 (1,4)	4 (2,7)	7 (4,12)	<0.001
Total charges (USD), median (IQR)	22,738 (13,225, 43,350)	34,869 (20,066, 66,424)	57,049 (33,103, 106,974)	<0.001

Abbreviations: AMI – Acute Myocardial Infarction; CABG – Coronary Artery Bypass Graft; IQR – Interquartile Range; PCI – Percutaneous Coronary Intervention; USD – United States Dollar.

A total of 1,511,495 patients were admitted with HF. 8,285 (0.5%) had a high HFRS, 535,650 (35.4%) had an intermediate HFRS and 967,524 (64.0%) had a low HFRS. Patients admitted for HF with a high HFRS were more likely to be older (median age 78 for high HFRS vs 75 for intermediate HFRS and 72 for low HFRS), female (59.9% for high HFRS vs 50.4% for intermediate HFRS and 46.6% for low HFRS). High HFRS patients with HF were more comorbid with conditions such as AF (37.5% for high HFRS vs 35.1% for intermediate HFRS and 29.9% for low HFRS), thrombocytopaenia (10.3% for high HFRS vs 7.1% for intermediate HFRS and 4.2% for low HFRS), anaemias (42.6% for high HFRS vs 34.7% for intermediate

HFRS and 20.0% for low HFRS), chronic renal failure (64.0% for high HFRS vs 56.0% for intermediate HFRS and 26.3% for low HFRS), and coagulopathy (13.8% for high HFRS vs 9.8% for intermediate HFRS and 5.6% for low HFRS) compared to patients with an intermediate or low HFRS (all p<0.001) (**Table** 4.20**).**

Table 4.20 Characteristics of patients admitted with heart failure.

Characteristics	Hospital Frailty Risk Score			p-value
	Low <5 (64.0%)	Intermediate 5-15 (35.4%)	High >15 (0.5%)	
Number of weighted discharges	967,524	535,650	8,285	
Age (years), median (IQR)	72 (59, 82)	75 (64, 85)	78 (68, 87)	<0.001
Female sex, %	46.6	50.4	59.9	<0.001
Ethnicity, %				<0.001
White	68.5	72.4	72.2	
Black	18.9	16.1	16.0	
Hispanic	7.7	6.9	7.0	
Other	4.9	4.6	4.8	
Weekend admission, %	22.8	23.4	22.7	<0.001
Primary expected payer, %				<0.001
Medicare	67.4	77.3	81.1	
Medicaid	12.5	8.9	6.8	
Private Insurance	14.2	10.4	8.9	
Self-pay	3.6	1.8	1.7	
No charge	0.3	0.1	0	
Other	2.1	1.6	1.5	
Median Household Income (percentile), %				<0.001
0-25th	34.3	32.1	29.3	
26th–50th	27.1	26.3	27.7	
51st-75th	22.4	23.5	22.5	
76th–100th	16.2	18.1	20.4	

Characteristics	Hospital Frailty Risk Score			p-value
	Low <5 (64.0%)	Intermediate 5-15 (35.4%)	High >15 (0.5%)	
Homelessness, %	1.0	0.6	0.2	<0.001
Comorbidities, %				
Atrial fibrillation	29.9	35.1	37.5	<0.001
Dyslipidaemia	40.3	45.5	44.2	<0.001
Thrombocytopenia	4.2	7.1	10.3	<0.001
Smoking	4.9	2.9	1.9	<0.001
Previous AMI	12.5	14.3	10.8	<0.001
Previous PCI	11.6	12.2	8.4	<0.001
Previous CABG	12.9	13.9	10.0	<0.001
Anaemias	20.0	34.7	42.6	<0.001
Valvular disease	14.7	15.6	14.3	<0.001
Hypertension	42.4	26.4	22.3	<0.001
Peripheral vascular disease	7.8	11.6	11.7	<0.001
Coagulopathy	5.6	9.8	13.8	<0.001
Diabetes Mellitus	37.4	41.3	38.5	<0.001
Liver disease	4.7	6.8	8.0	<0.001
Chronic renal failure	26.3	56.0	64.0	<0.001
Length of stay (days), median (IQR)	3 (2,5)	5 (3,8)	9 (6,16)	<0.001
Total charges (USD), median (IQR)	24,375 (14,278, 43,223)	36,362 (20,653, 68,004)	67,488 (35,573, 137,523)	<0.001

Abbreviations: AMI – Acute Myocardial Infarction; CABG – Coronary Artery Bypass Graft; IQR – Interquartile Range; PCI – Percutaneous Coronary Intervention; USD – United States Dollar.

A total of 375,940 patients were admitted with PE. 2,315 (0.6%) had a high HFRS, 95,240 (25.3%) had an intermediate HFRS and 278,385 (74.1%) had a low HFRS. Patients admitted for PE with a HFRS of >15 were more likely to be older (median age 76 for high HFRS vs 71 for intermediate HFRS and 63 for low HFRS) and female (57.5% for high HFRS vs 55.5% for

intermediate HFRS and 50.4% for low HFRS) and less likely to be white (63.0% for high HFRS vs 70.9% for intermediate HFRS and 71.4% for low HFRS). High risk patients with PE were more comorbid with conditions such as AF (24.8% for high HFRS vs 20.4% for intermediate HFRS and 10.7% for low HFRS), dyslipidaemia (46.0% for high HFRS vs 32.1% for intermediate HFRS and 34.6% for low HFRS), thrombocytopaenia (10.8% for high HFRS vs 8.8% for intermediate HFRS and 4.5% for low HFRS), anaemias (33.7% for high HFRS vs 30.0% for intermediate HFRS and 17.3% for low HFRS), hypertension (75.2% for high HFRS vs 73.1% for intermediate HFRS and 58.9% for low HFRS), coagulopathy (16.2% for high HFRS vs 14.1% for intermediate HFRS and 9.5% for low HFRS) and chronic renal failure (35.6% for high HFRS vs 27.8% for intermediate HFRS and 8.2% for low HFRS) compared to patients with an intermediate or low HFRS (all p<0.001) **(Table** 4.21**).**

Table 4.21 Characteristics of patients admitted with pulmonary embolism.

Characteristics	Hospital Frailty Risk Score			p-value
	Low <5 (74.1%)	**Intermediate 5-15 (25.3%)**	**High >15 (0.6%)**	
Number of weighted discharges	278,385	95,240	2,315	
Age (years), median (IQR)	63 (50, 73)	71 (60, 80)	76 (66, 83)	<0.001
Female sex, %	50.4	55.5	57.5	<0.001
Ethnicity, %				<0.001
White	71.4	70.9	63.0	
Black	19.0	19.6	25.9	
Hispanic	6.0	6.0	7.1	
Other	3.6	4.5	4.0	
Weekend admission, %	23.3	24.5	22.7	<0.001
Primary expected payer, %				<0.001
Medicare	47.5	68.3	77.5	
Medicaid	12.5	9.9	8.4	
Private Insurance	32.1	16.9	11.9	

Characteristics	Hospital Frailty Risk Score			p-value
	Low <5 (74.1%)	Intermediate 5-15 (25.3%)	High >15 (0.6%)	
Self-pay	4.7	2.6	0.9	
No charge	0.4	0.2	0.2	
Other	2.7	2.2	1.1	
Median Household Income (percentile), %				<0.001
0-25th	28.0	29.4	32.2	
26th–50th	26.7	26.2	26.7	
51st-75th	25.1	25.0	22.5	
76th–100th	20.2	19.3	18.6	
Homelessness, %	0.8	0.8	0.4	<0.096
Comorbidities, %				
Atrial fibrillation	10.7	20.4	24.8	<0.001
Dyslipidaemia	34.6	42.1	46.0	<0.001
Thrombocytopenia	4.5	8.8	10.8	<0.001
Smoking	16.2	10.8	6.3	<0.001
Previous AMI	4.7	6.5	5.8	<0.001
Previous PCI	4.7	5.6	3.2	<0.001
Previous CABG	2.9	3.9	3.0	<0.001
Anaemias	17.3	30.0	33.7	<0.001
Congestive heart failure	15.3	31.1	31.3	<0.001
Valvular disease	0.9	1.1	0.2	<0.001
Hypertension	58.9	73.1	75.2	<0.001
Peripheral vascular disease	4.0	6.8	7.8	<0.001
Coagulopathy	9.5	14.1	16.2	<0.001
Diabetes Mellitus	11.6	10.5	9.3	<0.001
Liver disease	3.5	7.4	7.3	<0.001
Chronic renal failure	8.2	27.8	35.6	<0.001
Length of stay (days), median (IQR)	3 (2,4)	5 (3,8)	8 (5,13)	<0.001

Characteristics	Hospital Frailty Risk Score			p-value
	Low <5 (74.1%)	Intermediate 5-15 (25.3%)	High >15 (0.6%)	
Total charges (USD), median (IQR)	27,980 (17,276, 48,897)	48,916, (28,155, 90,299)	79,458 (43,530, 147,753)	<0.001

Abbreviations: AMI – Acute Myocardial Infarction; CABG – Coronary Artery Bypass Graft; IQR – Interquartile Range; PCI – Percutaneous Coronary Intervention; USD – United States Dollar.

A total of 28,790 patients were admitted with cardiac arrest. 715 (2.5%) had a high HFRS, 20,275 (70.4%) had an intermediate HFRS and 7,800 (27.1%) had a low HFRS. Patients admitted for cardiac arrest with a high HFRS were more likely to be female (46.2% for high HFRS vs 42.7% for intermediate HFRS and 42.2% for low HFRS), less likely to be white (58.3% for high HFRS vs 61.9% for intermediate HFRS and 67.5% for low HFRS) and more comorbid with conditions such as AF (28.7% for high HFRS vs 27.3% for intermediate HFRS and 24.5% for low HFRS), dyslipidaemia (42.7% for high HFRS vs 33.3% for intermediate HFRS and 24.5% for low HFRS), thrombocytopaenia (14.0% for high HFRS vs 9.7% for intermediate HFRS and 3.8% for low HFRS), anaemias (42.7% for high HFRS vs 27.2% for intermediate HFRS and 13.1% for low HFRS), HF (52.4% for high HFRS vs 42.1% for intermediate HFRS and 29.2% for low HFRS), hypertension (81.1% for high HFRS vs 91.4% for intermediate HFRS and 58.7% for low HFRS), coagulopathy (15.4% for high HFRS vs 15.9% for intermediate HFRS and 5.5% for low HFRS) and chronic renal failure (56.6% for high HFRS vs 33.3% for intermediate HFRS and 16.0% for low HFRS) compared to patients with an intermediate and low HFRS (all p<0.001) **(**

Table 4.22**).**

Table 4.22 Characteristics of patients admitted with cardiac arrest.

Characteristics	Hospital Frailty Risk Score			p-value
	Low <5 (27.1%)	Intermediate 5-15 (70.4%)	High >15 (2.5%)	
Number of weighted discharges	7,800	20,275	715	
Age (years), median (IQR)	69 (57, 0)	67 (56, 77)	69 (59,77)	<0.001
Female sex, %	42.2	42.7	46.2	0.113
Ethnicity, %				<0.001
White	67.5	61.9	58.3	
Black	15.8	22.0	26.6	
Hispanic	10.6	9.0	10.1	
Other	6.1	7.1	5.0	
Weekend admission, %	24.9	29.0	23.8	<0.001
Primary expected payer, %				<0.001
Medicare	57.0	60.7	69.9	
Medicaid	11.3	14.1	15.4	
Private Insurance	20.9	16.6	10.5	
Self-pay	6.5	5.8	2.1	
No charge	0.3	0.2	<0.1	
Other	4.1	2.6	2.1	
Median Household Income (percentile), %				0.003
0-25th	32.9	33.6	36.9	
26th–50th	27.5	27.7	25.5	
51st-75th	21.2	22.0	22.7	
76th–100th	18.4	16.6	14.9	
Homelessness, %	0.3	0.7	<0.1	<0.001
Comorbidities, %				

Characteristics	Hospital Frailty Risk Score			p-value
	Low <5 (27.1%)	Intermediate 5-15 (70.4%)	High >15 (2.5%)	
Atrial fibrillation	24.5	27.3	28.7	<0.001
Dyslipidaemia	28.5	33.3	42.7	<0.001
Thrombocytopenia	3.8	9.7	14.0	<0.001
Smoking	14.3	15.0	11.9	0.032
Previous AMI	7.9	9.1	6.3	<0.001
Previous PCI	6.7	7.4	5.6	<0.001
Previous CABG	7.8	7.8	7.7	0.997
Anaemias	13.1	27.2	42.7	<0.001
Congestive heart failure	29.2	42.1	52.4	<0.001
Valvular disease	2.1	2.3	0.7	0.012
Hypertension	58.7	69.4	81.1	<0.001
Peripheral vascular disease	5.1	6.4	6.3	<0.001
Coagulopathy	5.5	15.9	15.4	<0.001
Diabetes Mellitus	15.1	10.0	9.1	<0.001
Liver disease	9.6	22.7	14.7	<0.001
Chronic renal failure	16.0	33.3	56.6	<0.001
Length of stay (days), median (IQR)	1 (0,2)	2 (1,6)	7 (3,15)	<0.001
Total charges (USD), median (IQR)	30,888 (16,489, 60,798)	60,331 (31,517, 117,913)	119,279 (50,727, 249,569)	<0.001

Abbreviations: AMI – Acute Myocardial Infarction; CABG – Coronary Artery Bypass Graft; IQR – Interquartile Range; PCI – Percutaneous Coronary Intervention; USD – United States Dollar.

A total of 545, 695 patients were admitted with acute haemorrhagic stroke. 49,855 (9.1%) had a high HFRS, 299,620 (54.9%) had an intermediate HFRS, and 196,220 (36.0%) had a low HFRS. Patients admitted for acute haemorrhagic stroke with a high HFRS were more likely to be female (48.9% for high HFRS vs 48.5% for intermediate HFRS and 47.8% for low HFRS).

High HFRS patients with acute haemorrhagic stroke were more comorbid with conditions such as AF (18.4% for high HFRS vs 17.9% for intermediate HFRS and 14.6% for low HFRS), thrombocytopaenia (7.9% for high HFRS vs 6.6% for intermediate HFRS and 4.6% for low HFRS), anaemias (25.6% for high HFRS vs 18.1% for intermediate HFRS and 9.4% for low HFRS), hypertension (73.4% for high HFRS vs 71.0% for intermediate HFRS and 66.9% for low HFRS), coagulopathy (14.1% for high HFRS vs 12.0% for intermediate HFRS and 8.6% for low HFRS), PVD (5.3% for high HFRS vs 4.8% for intermediate HFRS and 3.6% for low HFRS) and chronic renal failure (25.4% for high HFRS vs 17.7% for intermediate HFRS and 7.3% for low HFRS) compared to patients with an intermediate and low HFRS (p<0.001) **(Table** 4.23**).**

Table 4.23 Characteristics of patients admitted with acute haemorrhagic stroke.

Characteristics	Hospital Frailty Risk Score			p-value
	Low <5 (36.0%)	**Intermediate 5-15 (54.9%)**	**High >15 (9.1%)**	
Number of weighted discharges	196,220	299,620	49,855	
Age (years), median (IQR)	68 (56, 79)	69 (57, 80)	68 (56, 78)	<0.001
Female sex, %	47.8	48.5	48.9	<0.001
Ethnicity, %				<0.001
White	65.2	61.9	54.9	
Black	14.6	17.8	21.9	
Hispanic	11.3	10.8	12.5	
Other	8.9	9.5	10.7	
Weekend admission, %	25.2	26.7	26.7	<0.001
Primary expected payer, %				<0.001
Medicare	54.7	60.0	56.5	
Medicaid	10.5	12.1	15.7	
Private Insurance	25.8	20.3	20.4	
Self-pay	5.3	4.8	5.1	

Characteristics	Hospital Frailty Risk Score			p-value
	Low <5 (36.0%)	Intermediate 5-15 (54.9%)	High >15 (9.1%)	
No charge	0.4	0.3	0.3	
Other	3.5	2.6	2.0	
Median Household Income (percentile), %				<0.001
0-25th	28.5	30.0	31.2	
26th–50th	25.4	25.0	24.4	
51st-75th	24.0	23.9	23.7	
76th–100th	22.0	21.1	20.7	
Homelessness, %	0.3	0.4	0.4	<0.001
Comorbidities, %				
Atrial fibrillation	14.6	17.9	18.4	<0.001
Dyslipidaemia	35.1	39.0	37.7	<0.001
Thrombocytopenia	4.6	6.6	7.9	<0.001
Smoking	6.8	7.6	8.6	<0.001
Previous AMI	4.4	5.1	4.4	<0.001
Previous PCI	4.9	5.2	3.3	<0.001
Previous CABG	4.2	4.5	3.3	<0.001
Anaemias	9.4	18.1	25.6	<0.001
Congestive heart failure	9.2	14.2	16.3	<0.001
Valvular disease	2.3	2.6	2.1	<0.001
Hypertension	66.9	71.0	73.4	<0.001
Peripheral vascular disease	3.6	4.8	5.3	<0.001
Coagulopathy	8.6	12.0	14.1	<0.001
Diabetes Mellitus	19.6	20.2	16.3	<0.001
Liver disease	2.8	3.7	3.5	<0.001
Chronic renal failure	7.3	17.7	25.4	<0.001
Length of stay (days), median (IQR)	3 (2,6)	6 (3,12)	13 (7,23)	<0.001

Characteristics	Hospital Frailty Risk Score			p-value
	Low <5 (36.0%)	Intermediate 5-15 (54.9%)	High >15 (9.1%)	
Total charges (USD), median (IQR)	44,331 (22,024, 93452)	71,806 (34,640, 167,091)	162,137 (71,932, 342,705)	<0.001

Abbreviations: AMI – Acute Myocardial Infarction; CABG – Coronary Artery Bypass Graft; IQR – Interquartile Range; PCI – Percutaneous Coronary Intervention; USD – United States Dollar.

A total of 6,949,960 patients were admitted for 'Other CVD'. 77,525 (1.1%) had a high HFRS, 2,411,675 (34.7%) had an intermediate HFRS, and 4,460,760 (64.2%) had a low HFRS. Patients admitted for 'Other CVD' with a high HFRS were more likely to be older (median age 75 for high HFRS vs 72 for intermediate HFRS and 68 for low HFRS) and female (56.2% for high HFRS vs 47.7% for intermediate HFRS and 41.6% for low HFRS). High HFRS patients with 'Other CVD' were more comorbid with conditions such as thrombocytopaenia (8.8% for high HFRS vs 8.1% for intermediate HFRS and 5.0% for low HFRS), anaemias (39.1% for high HFRS vs 38.6% for intermediate HFRS and 18.9% for low HFRS) and coagulopathy (11.1% for high HFRS vs 10.0% for intermediate HFRS and 6.2% for low HFRS), compared to patients with an intermediate and low HFRS (all p<0.001) **(Table** 4.24**).**

Table 4.24 Characteristics of patients admitted with other cardiovascular diseases.

Characteristics	Hospital Frailty Risk Score			p-value
	Low <5 (64.2%)	Intermediate 5-15 (34.7%)	High >15 (1.1%)	
Number of weighted discharges	4,460,760	2,411,675	77,525	
Age (years), median (IQR)	68 (58, 78)	72 (62, 82)	75 (66, 84)	
Female sex, %	41.6	47.7	56.2	<0.001
Ethnicity, %				<0.001
White	70.0	66.3	67.2	
Black	15.6	19.4	18.9	

Characteristics	Hospital Frailty Risk Score			p-value
	Low <5 (64.2%)	Intermediate 5-15 (34.7%)	High >15 (1.1%)	
Hispanic	8.7	8.8	8.3	
Other	5.6	5.5	5.6	
Weekend admission, %	17.2	20.6	19.3	<0.001
Primary expected payer, %				<0.001
Medicare	61.9	73.6	77.9	
Medicaid	10.6	9.6	7.9	
Private Insurance	21.2	12.6	11.1	
Self-pay	3.5	2.2	1.6	
No charge	0.3	0.2	0.1	
Other	2.5	1.9	1.4	
Median Household Income (percentile), %				<0.001
0-25th	31.2	31.9	29.7	
26th–50th	26.7	26.3	25.8	
51st-75th	23.5	23.5	24.4	
76th–100th	18.6	18.2	20.0	
Homelessness, %	0.6	0.7	0.3	<0.001
Comorbidities, %				
Atrial fibrillation	26.3	37.4	27.8	<0.001
Dyslipidaemia	59.9	57.7	55.7	<0.001
Thrombocytopenia	5.0	8.1	8.8	<0.001
Smoking	14.4	11.1	7.8	<0.001
Previous AMI	15.2	14.1	9.8	<0.001
Previous PCI	17.0	13.2	7.9	<0.001
Previous CABG	11.7	11.3	7.4	<0.001
Anaemias	18.9	38.6	39.1	<0.001
Congestive heart failure	46.5	65.2	51.9	<0.001
Valvular disease	4.7	4.7	3.4	<0.001
Hypertension	81.3	88.6	88.2	<0.001

Characteristics	Hospital Frailty Risk Score			p-value
	Low <5 (64.2%)	Intermediate 5-15 (34.7%)	High >15 (1.1%)	
Peripheral vascular disease	14.1	13.7	13.6	<0.001
Coagulopathy	6.2	10.0	11.1	<0.001
Diabetes Mellitus	20.6	11.2	9.4	<0.001
Liver disease	3.3	5.9	4.9	<0.001
Chronic renal failure	23.2	57.4	54.2	<0.001

Abbreviations: AMI – Acute Myocardial Infarction; CABG – Coronary Artery Bypass Graft; IQR – Interquartile Range; PCI – Percutaneous Coronary Intervention; USD – United States Dollar.

4.3.4 Discussion

4.3.4.1 Main findings

This national analysis of CVD hospitalisations stratified by HFRS has several important main findings. Firstly, we report the most common CVD admissions across frailty categories, with AMI being the most common in patients with a low frailty score, and acute ischaemic stroke being the most common in patients with an intermediate and high frailty score. Secondly, we report important frailty-based differences in baseline characteristics across patients with different CVD admission diagnoses. Finally, patients with an intermediate and high frailty score had increased all-cause mortality compared with their counterparts with lower risk across most CVD admission diagnoses, except in cardiac arrest and acute haemorrhagic stroke categories.

4.3.4.2 Prevalence of frailty

The HFRS was nationally validated using a cohort of over 1 million UK patients, of which 37.6% had an intermediate risk of frailty and 20% had a high risk of frailty [10]. We report a

lower proportion of patients at intermediate or high risk of frailty in this cohort of 9 million patients hospitalised with CVD in the US. The prevalence of frailty amongst overall CVD patients has been previously estimated between 15% and 19% [9, 16, 177], and up to as much as 40.9% in studies utilising HFRS [101, 102]. As stated in previous chapters, the reported prevalence of frailty varies due to its lack of standardised definition and assessment. The HFRS follows the deficit model (combining impairments) and has been validated against the Rockwood and Fried scores. It is an advantageous option as it is dependent on the ICD coding system [178], however it can be quite challenging for clinicians to calculate due to lack of automated computation [90]. This study observed that patients with increasing frailty are likely to be older, female, from a non-white ethnic group, have longer hospital stays and total costs, as reported extensively in previous studies [3, 10, 16, 21, 90, 102].

4.3.4.3 Frailty and cardiovascular disease admissions

Amongst patients with intermediate or high frailty risk, the most prevalent CVD admission was acute ischaemic stroke. Stroke and its sequalae are included in the HFRS, however, other contributors are important. For example, older age increases the risk of both stroke and frailty, with 70% of strokes occurring after the age of 65 [55]. AF has been reported to be prevalent in 15% of the frail population, which is what was observed in this study, however, the mentioned study observed a decreasing proportion of AF admission with increasing frailty [164]. This could be mediated by the definition of frailty as the study used scores devised by *Fried et al.* and *Rockwood et al.* [164]. Studies using the HFRS demonstrated most patients with AF had a low risk of frailty, with a small percentage at high risk, similar to this study [179]. This study shows admission for HF decreases with increasing frailty yet is still common with over 3 in 10 patients admitted with HF at intermediate or high risk of frailty. This was demonstrated in other studies where intermediate or high risk of frailty was present in up to 20% of hospitalised HF

patients and is associated with a longer length of stay and increased total charges [90, 103]. This could be explained by an increased number of comorbidities in the HF population, with a high prevalence of dyslipidaemia, anaemia, and hypertension [90]. This agrees with multiple studies that demonstrate patients with increased HFRS have higher Charlson comorbidity score, in line with the HFRS being based on the total comorbidity burden of patients [10, 90, 102]. There are no studies describing the prevalence of PE, cardiac arrest, and acute haemorrhagic stroke among hospitalised frail patients.

4.3.4.4 Frailty and mortality

AF was a rare cause of admission in the high-risk group. Interestingly, crude mortality rates in patients with AF was low, however the prognostic impact of frailty in high risk patients was greatest of all CVD admission groups, when compared to low frailty risk counterparts. The association between AF and mortality has been reported in multiple studies, as the prevalence of AF increases with age, comorbidity burden, and increases the risk of stroke and its associated complications [162, 163]. Studies have suggested that patients with frailty also have a larger left atrial volume, which is one of the main cardiac abnormalities linked to the development of AF and systolic dysfunction [180]. Furthermore, patients with incident AF are commonly anticoagulated, which may increase the risk of bleeding and further complications such as haemorrhage [162]. However, studies report that AF patients with increasing frailty are less likely to be treated with oral anticoagulants, which can lead to increased likelihood of downstream thrombotic events and poorer outcomes [179, 180]. In addition, HF was independently associated with higher odds of mortality with increasing frailty as seen in other studies [90, 103]. Our findings of lower odds of mortality of increasingly frail patients admitted with cardiac arrest and acute haemorrhagic stroke, whilst different to the other CVD admissions of interest, could have several explanations. These conditions have substantial mortality *per se*

and could be associated with concomitant conditions that are not accountable in the HFRS. For example, cardiac arrest could be associated with different reversible conditions that influence short-term prognosis [181, 182]. This analysis encompassed only patients that were admitted due to cardiac arrest leading to potential selection bias as it is unknown how many patients suffered out-of-hospital cardiac arrest and did not arrive to hospital. Therefore, it is possible that the poor outcomes in these patient groups occur independent of frailty status [69, 183], or that the frailest patients do not survive to admission, which may reduce any effect size.

4.3.4.5 Clinical implications

There are important clinical implications of this study. This study demonstrates that patients with intermediate to high frailty risk represent a substantial portion of population admitted for CVD and raises the importance of frailty assessment by cardiologists. A co-existence of frailty and CVD is becoming even more important due to an aging population with higher morbidity burden. Frail patients admitted with CVD have higher mortality rates and burden the healthcare system, and knowledge of the trends in CVD admission is fundamental to improve the outcomes of this clinically at-risk population. This study may support the early identification and management of CVD in frail patients, particular in primary care, although whether this would impact on acute admissions is unknown.

4.3.4.6 Limitations

This study has several limitations inherent to the use of the NIS database. Firstly, coded data for the NIS could be subject to selection bias due to inaccurate coding or missing data. Secondly, detailed clinical information such as pharmacological treatment that can mediate outcomes could not be investigated due to their lack of availability with the NIS. The impact of differential pharmacological management in the frail population on outcomes may be an area for further research. Thirdly, as this is an observational study, confounding bias could not

be fully eliminated despite the broad scope of conditions covered by the NIS, and therefore causality between frailty, CVD admission and mortality cannot be proven. Fourthly, we used a single measure of frailty and outcomes may not be relevant in the context of other models to assess frailty. Finally, the NIS only captures information on in-hospital events and therefore, more detailed analysis of longitudinal outcomes could not be assessed [184].

4.3.5 Conclusion

In conclusion, the causes of CVD admission vary with frailty status with AMI being the most common in patients with a low risk of frailty, whereas acute ischaemic stroke being most common in patients with intermediate or high risk of frailty. Increasing frailty in patients admitted for AMI, acute ischaemic stroke, AF, HF and PE is associated with an increased all-cause mortality. Future, more granular studies are necessary to guide care and improve the CVD outcomes in frail patients in an ever-aging population.

4.4 Chapter summary

This chapter summarised the two studies conducted to investigate the aims of this thesis. The first investigated the causes and outcomes of CVD in frail patients admitted in the ED using the NEDS. The second investigated the causes and outcomes of CVD in frail patients admitted to hospital using the NIS.

5. Chapter 5: General discussion

5.1 Chapter overview

This thesis aimed to investigate the association of frailty status with the prevalence, clinical characteristics, and outcomes of patients CVD. Results of the studies included in this thesis have been discussed in detail in prior chapters. Therefore, this chapter provides a general overview of the key results of the thesis. Following this, the strengths and limitations, clinical implications and areas of future research arising from this thesis is outlined.

5.2 Aims investigated

This thesis is comprised of a systematic review and 2 studies to investigate the aforementioned aims. The first study used the NEDS, and the second study used the NIS, reporting 1) the prevalence of frailty in CVD patients in the ED and in-patient setting, 2) the clinical characteristics of frail patients with CVD encountered in the ED or admitted to hospital, 3) the discharge disposition from the ED in CVD patients with frailty and 4) the crude rates and adjusted odds of mortality from CVD in patients with frailty in the ED and hospital setting.

5.3 Main findings

5.3.1 Emergency department encounters

There were several key findings from the ED CVD cohort stratified by HFRS category. Firstly, frailty risk as measured by the HFRS represents a significant proportion of ED encounters for CVD, with almost 40% of patients either at intermediate or high risk of frailty. Secondly this

study found important differences in CVD phenotypes in frail patients presenting to the ED. Of the selected CVD, ischaemic stroke was the most common reason for encounter in the high HFRS group, followed by haemorrhagic stroke and AMI. For the low HFRS group, cardiac arrest was the most common reason for encounter followed by AF and AMI. Thirdly, increasing HFRS category was associated with older age, female sex and higher prevalence of comorbidities. Finally, this study found that increasing HFRS category was associated with increased odds of adverse outcomes amongst most CVD, in comparison to the low HFRS group, with increasing frailty associated with decreased ED mortality but increased in-hospital mortality.

5.3.2 Hospital admissions

There were several key findings from the hospitalised CVD cohort stratified by HFRS category. Firstly, frailty is present in a significant proportion of hospitalised patients with CVD, with around 40% of patients either at intermediate or high risk of frailty. Secondly, there are important trends in CVD phenotypes amongst frailty risk categories. Acute ischaemic stroke was the most common in patients with an intermediate and high HFRS and AMI was the most common in patients with a low HFRS. Thirdly, this study found patients with increasing HFRS are more likely to be older and female, as reported in many other frailty studies. Finally, patients with increasing frailty were had an increased odds of all-cause mortality across most CVD, except for cardiac arrest and acute haemorrhagic stroke. The highest odds of mortality were observed in high HFRS patients admitted with AF.

5.3.3 Comparison of findings

Although this analysis did not include a direct comparison of ED and inpatient cohorts, it is valuable to relatively compare the findings amongst each cohort. There were several

similarities and differences between ED encounters and hospital admissions for CVD. Firstly, the ED group had a higher proportion of patients at high risk of frailty, with the proportion of patients at intermediate risk of frailty higher in the hospitalised group and the proportion of low frailty risk patients similar between both groups. Secondly, increasing frailty was associated with similar clinical characteristics across both ED encounters and hospital admissions such as increased age, female sex, comorbidities, total charges and length of stay. Thirdly, acute ischaemic stroke was the most common cause of selected CVD admission for intermediate and high risk patients in both ED and hospitalised patients. However, in low risk patients, AF was the most common admission for the ED group whereas AMI was the most common admission for the hospitalised group. This could be due to AF and AMI being common in low frailty risk patients across both groups, yet AMI is more likely to lead to hospitalisation in comparison to patients with AF. Fourthly, in the ED study, acute ischaemic stroke, acute haemorrhagic stroke, AMI and HF had the highest proportions of patients at high risk of frailty, which was similar to hospitalisations where acute ischaemic stroke, acute haemorrhagic stroke and cardiac arrest had the highest proportions of high frailty risk patients. Fifthly, acute haemorrhagic stroke and cardiac arrest were observed to have unexpected outcomes with increasing frailty, with improved or minimally worse outcomes in both the ED and hospital setting. This could be due to the inherent poor prognosis of both conditions, but also due to a selection bias of cases where more robust patients survive until ED encounter and hospitalisation. Sixthly, AF was associated with the largest effect size of worse outcomes in both settings for highly frail patients despite a low proportion of AF patients at high risk. This could be due AF being a condition of older age and associated with devastating comorbidities such as acute ischaemic stroke and increased likelihood of anticoagulant use can lead to other adverse events such as acute haemorrhagic stroke. Finally, whilst across most CVD the crude and adjusted odds of mortality in the ED decreased with increasing frailty, hospital mortality

increased in both settings, which could reflect identification of frailty at an early stage of ED encounter leading to increased likelihood of admission where worse outcomes occurred.

5.4 Clinical implications

The results from these studies provide important information which adds to the growing body of evidence about the association between CVD and frailty. This may have several important clinical implications. Firstly, this thesis demonstrates that intermediate to high frailty risk is present in a significant proportion of the population admitted with acute CVD. The population is ageing and increasing in morbidity burden, therefore, the relationship between frailty and CVD is becoming even more important. Moreover, their co-existence in an ageing population has significant ramifications for healthcare services. Knowledge of the prevalence and tools to stratify frailty risk is fundamental to adapt services to the needs of the frail population. Examples of changes can include enhanced care in care homes, a tailored direct access to healthcare for frail patients in the community and community teams to identify patients at an earlier stage with frailty and provide proactive care [185, 186]. Secondly, this thesis demonstrated that overall, increasing frailty is associated with increased likelihood of certain clinical characteristics, such as age, female sex and non-white race. It is important to highlight disparities in care and identify areas of further research to reduce these disparities. Thirdly, the distribution of frailty differs depending on CVD phenotype. Knowledge of the trends in CVD admission is fundamental to improve the outcomes of this clinically at-risk population. Fourthly, frail patients with CVD generally have higher mortality rates, raising the importance of frailty assessment by the healthcare team. Frailty assessments have a positive effect on outcomes in a variety of clinical settings. Early identification and risk stratification of frailty is patients with CVD can result in early provision of treatment, optimisation of risk factors, delayed progression to frailty, potential reversal of frailty, improvement in downstream

physical and quality of life outcomes and reduced rates of readmission and death. Key members of the core healthcare team involved include general cardiologists, general practitioners and nurses [187]. General practitioner and nurses could be fundamental to identifying frailty in the community setting. Once identifying frailty, general practitioners can be involved with providing key patient information, optimising risk factors escalating to specialist physicians and general monitoring and clinical management of frailty in primary care, which can also prevent progression or encourage primordial prevention in patients at risk but not yet frail [187]. Nursing teams can provide more personalised and holistic care of frail patients to prevent deconditioning through patient education and interventions such as exercise and rehabilitation to prevent progression of frailty [187]. Cardiologists could be involved in the specific management of CVD conditions in patients with frailty once it has been identified in primary care [187]. In the secondary care setting, this role can involve individualised assessments of patients at risk of frailty (which can also involve geriatricians), optimising of CVD specific risk factors and encouraging CVD prevention practices in patients at risk [187]. Moreover, evidence suggests that frail patients may benefit from prehabilitation, leading to improved morbidity after elective surgery, with multimodal prehabilitation conferring a greater benefit that single modal interventions such as exercise alone [188-190]. Furthermore, there is evidence of reversibility or prevention of frailty in HF patients through the use of rehabilitation strategies [173, 191]. However, there is sparse evidence about the benefits of rehabilitation in frail patients with other CVD. Many trials and still in progress and evidence can still be limited by the heterogeneity of frailty measures in use [173]. Based on the current evidence, interventions (e.g. physical, pharmacological, nutritional, cognitive and social) for frailty could confer a positive benefit to frail patients with other CVD, potentially leading to a halt in the progression or even reversal of frailty and improved outcomes if admitted with complications [173].

5.5 Future research

This thesis identified potential areas of future research. Firstly, through the literature search that were carried out to identify well reported areas of research and to identify novel areas to pursue on the topic of CVD and frailty, we found few studies used the HFRS in CVD cohorts. Most studies opted for either the CFS, FI, FP or objective measures such as walking speed and handgrip strength. Further research into the prognostic capabilities of the HFRS on a CVD cohort, in the form of observational studies such as the ones conducted in this thesis, would be warranted, particularly in areas beyond the US. This would be important as many countries and hospitals move towards routine EHR data collection in the form of registries like the Acute myocardial infarction National Audit Project (MINAP) and British cardiovascular Intervention Society (BCIS) cardiology specific datasets in the UK, or more general datasets such as the Clinical Practice Research Datalink, and the NEDS and NIS used in this thesis. Secondly, further work investigating the mechanistic links between CVD and frailty would be warranted. It is important to understand the underlying mechanisms to target at-risk patients and optimise management strategies in the acute setting. Currently, the literature speculates as to their association, but specific mechanistic links between frailty and different CVD would aid healthcare delivery for CVD patients. Thirdly, as mentioned, the studies included in this thesis were not able to investigate the impact of pharmacological treatment. Pharmacological treatment of CVD can mediate causes of admission and outcomes. Therefore, more granular analysis of frailty in the CVD setting, using pharmacological data such as dosage and treatment duration, could identify areas of improvement of care, and whether such treatment is effective in frail patients. Currently, treatment such as anticoagulants for AF are withheld in patients with a high falls risk, which is seen in a significant number of frail patients. However, as this thesis has found, AF was associated with the highest odds of mortality across all the CVD of interest. Therefore, it would be important to determine whether the benefits of anticoagulation

outweigh the risk of bleeding in at-risk patient groups. Fourthly, our studies were unable to follow-up patients due to the NIS only containing data on in-hospital mortality. It would be important to investigate the longitudinal outcomes in frail patients that do survive ED or hospital encounters for their CVD. As with pharmacological management, this information would aid healthcare services in planning healthcare around the growing needs of the ageing population. Finally, further sex and race disaggregated analysis of the outcomes of frail patients admitted with CVD would be warranted to reduce disparities in care within patient populations and demographics. Currently, there is little data investigating the reasons behind worse outcomes in female and black patients, however there is a growing body of evidence in cardiovascular medicine that this is the case.

5.6 Strengths and limitations

5.6.1 Databases

Both studies have strengths and limitations inherent to the use of both databases. The NEDS and NIS have several strengths. Firstly, they are both the largest available database of ED encounters and hospital admissions in the US [142]. Larger datasets allow more precise estimates in comparison to smaller datasets and are particularly useful when investigating rare diseases, or small relationships. Secondly, both datasets represent a stratified sample of the US, including hospitals of varying characteristics. A representative, population-based sample ensures improved external validity and generalisability of results. The breadth and depth of variables included in both datasets is thorough, thus further contributing to improved validity and generalisability of results. Many variables were included to describe the clinical characteristics of frail patients in both studies, and many of those variables were included in the adjusted analysis to improve the performance of the model used to assess the odds of mortality [142].

However, both databases have limitations. Firstly, as outlined in Chapter 3, there is bias involved in these studies, inherent to each of the databases used. These biases and their associated effects have been outlined in Chapter 3. Briefly, the first bias demonstrated in this study can be divided into negative and unmeasured confounding. Negative confounding occurs when a variable used in the model is bias towards the null hypothesis, and therefore the overall effect is underestimated. This contrasts with positive confounding where there is bias towards the null hypothesis, overestimating the overall effect. In both studies, age was adjusted for in the logistic regression model, despite age being one of the strongest risk factors of frailty. Therefore, this study could have underestimated the relationship between CVD and frailty, particularly given many of the CVD of interest also have a strong association with age. Unmeasured confounding is defined as the omission of data that is relevant to the study and could have affected this thesis' results. Both databases do not collect data on pharmacological treatment, which could have been used in the logistic regression model or to further stratify patients for a more granular analysis [149, 150]. Multiple studies have explored the effect of medications on outcomes of cardiovascular disease and its associated outcomes and other studies have investigated the impact of medications and polypharmacy on frail patients. Inclusion of this data would have been useful to investigate the impact of medications and polypharmacy and determine whether treatment of CVD in the elderly is has an impact on frailty, or vice-versa [103]. More granular studies including this treatment should be considered in future research in this area. Secondly the use of coded data is subject to selection bias due to inaccurate coding or missing data, this is however, minimised by the board scope of conditions covered by both databases [149, 150]. This was a major limitation for the ED study, as race is not available on the NEDS and therefore could not be adjusted for in the regression analysis. The effect of race on the management and outcomes of patients not only in CVD but across many specialities and countries is an important topic [72, 192-194]. Thirdly, both databases

only capture episodes of care, and therefore cannot account for multiple readmissions. It would be beneficial to adjust for multiple admissions, readmissions for the same pathology or investigate first-time admissions. This would have provided further insight into the effect of frailty on future cardiovascular health and outcomes. Finally, both datasets only capture information on the current episode, be it in the ED or in-hospital and therefore, more detailed analysis of longitudinal outcomes cannot be assessed. Longitudinal outcomes are needed to assess the long-term implications of hospital admissions and their associated outcomes out-of-hospital [184]. Finally, the HFRS was developed and validated on a UK cohort. This thesis used the HFRS with data for US hospitalisations. However, this score has been utilised and externally validated in many non-UK countries [195-197].

5.6.2 Study design

Both studies were observational, more specifically, retrospective cohort studies. There are several strengths and limitations to retrospective observational studies, which were briefly described in Chapter 3. In terms of strengths, firstly, the exposure occurs before the outcome [198]. In this case, each study was able to stratify CVD patients by their HFRS, before they had died. Secondly, given the broad array of variables included in the NIS, each study was able to assess multiple exposures on the outcome of mortality, such as age, socio-economic status, hospital characteristics and comorbidities. Finally, these studies have could assess multiple outcomes simultaneously, to provide a broader scope of the burden of frailty in the CVD population. In both studies, prevalence, clinical characteristics, and mortality were ascertained and in the NEDS analysis specifically, discharge disposition enabled useful insight into the effect of frailty.

Limitations of retrospective cohort studies come from the nature of the data. As it's retrospective, other useful variables (such as the aforementioned medications used) cannot be

gathered. Therefore, the analysis is limited by the data available. Secondly, cohort studies can only investigate associations and not causality. This means that the a variable that seemingly contributes to the outcome of interest may be explained by an interplay of other variables also known as confounders [198]. Finally, diagnosis codes are generated upon discharge and therefore, it is unknown whether diagnosis codes are referring to a pathology present prior to admission or because of the admission, giving rise to uncertainty in associations.

5.7 Chapter summary

This chapter provided a general discussion about the studies conducted to investigate the aims of this thesis. The studies found that frailty represents a significant proportion of the population with CVD. Frailty is associated with increased odds of adverse outcomes in both an ED and hospital setting. This chapter outlined the strengths and limitations, clinical implications and potential areas of further research as a result of this thesis.

5.8 Thesis conclusion

In conclusion, this thesis investigated the relationship between CVD and frailty in the secondary care setting using routinely collected EHR data from the US. The NEDS and NIS were used to identify all hospitalisations for CVD, further stratifying into 7 CVD of interest: AMI, acute ischaemic stroke, AF, HF, PE, cardiac arrest, and acute haemorrhagic stroke. These patients were then stratified by their HFRS into 3 frailty risk categories: low, intermediate, and high risk. These studies found that frail patients represent a significant proportion of the population admitted with CVD. These patients were more likely to be older, female and have more comorbidities. Patients with a high HFRS were associated with increased odds of mortality across most CVD diagnoses of interest. These studies re-affirm that frailty incurs a significant healthcare burden.

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Appendices

Appendix 1. Components of Hospital Frailty Risk Score with associated weighting.

Hospital Frailty Risk Score Variables	Codes	Source	Weighting
Dementia in Alzheimer's disease	F00	ICD-10	7.1
Hemiplegia	G81	ICD-10	4.4
Alzheimer's disease	G30	ICD-10	4
Sequelae of cerebrovascular disease	I69	ICD-10	3.7
Other symptoms and signs involving the nervous and musculoskeletal systems	R29	ICD-10	3.6
Other disorders of urinary system (includes urinary tract infection and urinary incontinence)	N39	ICD-10	3.2
Delirium, not induced by alcohol and other psychoactive substances	F05	ICD-10	3.2
Unspecified fall	W19	ICD-10	3.2
Superficial injury of head	S00	ICD-10	3.2
Unspecified haematuria	R31	ICD-10	3
Other bacterial agents as the cause of diseases classified to other chapters	B96	ICD-10	2.9
Other symptoms and signs involving cognitive functions and awareness	R41	ICD-10	2.7
Abnormalities of gait and mobility	R26	ICD-10	2.6
Other cerebrovascular diseases	I67	ICD-10	2.6
Convulsions, not elsewhere classified	R56	ICD-10	2.6
Somnolence, stupor and coma	R40	ICD-10	2.5
Complications of genitourinary prosthetic devices, implants and grafts	T83	ICD-10	2.4
Intracranial injury	S06	ICD-10	2.4
Fracture of shoulder and upper arm	S42	ICD-10	2.3
Other disorders of fluid, electrolyte and acid- base balance	E87	ICD-10	2.3
Other joint disorders, not elsewhere classified	M25	ICD-10	2.3
Volume depletion	E86	ICD-10	2.3
Senility	R54	ICD-10	2.2
Care involving use of rehabilitation procedures	Z50	ICD-10	2.1
Unspecified dementia	F03	ICD-10	2.1

Other fall on same level	W18	ICD-10	2.1
Problems related to medical facilities and other health care	Z75	ICD-10	2
Vascular dementia	F01	ICD-10	2
Superficial injury of lower leg	S80	ICD-10	2
Cellulitis	L03	ICD-10	2
Blindness and low vision	H54	ICD-10	1.9
Deficiency of other B group vitamins	E53	ICD-10	1.9
Problems related to social environment	Z60	ICD-10	1.8
Parkinson's disease	G20	ICD-10	1.8
Syncope and collapse	R55	ICD-10	1.8
Fracture of rib(s), sternum and thoracic spine	S22	ICD-10	1.8
Other functional intestinal disorders	K59	ICD-10	1.8
Acute renal failure	N17	ICD-10	1.8
Decubitus ulcer	L89	ICD-10	1.7
Carrier of infectious disease	Z22	ICD-10	1.7
Streptococcus and staphylococcus as the cause of diseases classified to other chapters	B95	ICD-10	1.7
Ulcer of lower limb, not elsewhere classified	L97	ICD-10	1.6
Other symptoms and signs involving general sensations and perceptions	R44	ICD-10	1.6
Duodenal ulcer	K26	ICD-10	1.6
Hypotension	I95	ICD-10	1.6
Unspecified renal failure	N19	ICD-10	1.6
Other septicaemia	A41	ICD-10	1.6
Personal history of other diseases and conditions	Z87	ICD-10	1.5
Respiratory failure, not elsewhere classified	J96	ICD-10	1.5
Exposure to unspecified factor	X59	ICD-10	1.5
Other arthrosis	M19	ICD-10	1.5
Epilepsy	G40	ICD-10	1.5
Osteoporosis without pathological fracture	M81	ICD-10	1.4
Fracture of femur	S72	ICD-10	1.4
Fracture of lumbar spine and pelvis	S32	ICD-10	1.4
Other disorders of pancreatic internal secretion	E16	ICD-10	1.4
Abnormal results of function studies	R94	ICD-10	1.4

Chronic renal failure	N18	ICD-10	1.4
Retention of urine	R33	ICD-10	1.3
Unknown and unspecified causes of morbidity	R69	ICD-10	1.3
Other disorders of kidney and ureter, not elsewhere classified	N28	ICD-10	1.3
Unspecified urinary incontinence	R32	ICD-10	1.2
Other degenerative diseases of nervous system, not elsewhere classified	G31	ICD-10	1.2
Nosocomial condition	Y95	ICD-10	1.2
Other and unspecified injuries of head	S09	ICD-10	1.2
Symptoms and signs involving emotional state	R45	ICD-10	1.2
Transient cerebral ischaemic attacks and related syndromes	G45	ICD-10	1.2
Problems related to care-provider dependency	Z74	ICD-10	1.1
Other soft tissue disorders, not elsewhere classified	M79	ICD-10	1.1
Fall involving bed	W06	ICD-10	1.1
Open wound of head	S01	ICD-10	1.1
Other bacterial intestinal infections	A04	ICD-10	1.1
Diarrhoea and gastroenteritis of presumed infectious origin	A09	ICD-10	1.1
Pneumonia, organism unspecified	J18	ICD-10	1.1
Pneumonitis due to solids and liquids	J69	ICD-10	1
Speech disturbances, not elsewhere classified	R47	ICD-10	1
Vitamin D deficiency	E55	ICD-10	1
Artificial opening status	Z93	ICD-10	1
Gangrene, not elsewhere classified	R02	ICD-10	1
Symptoms and signs concerning food and fluid intake	R63	ICD-10	0.9
Other hearing loss	H91	ICD-10	0.9
Fall on and from stairs and steps	W10	ICD-10	0.9
Fall on same level from slipping, tripping and stumbling	W01	ICD-10	0.9
Thyrotoxicosis [hyperthyroidism]	E05	ICD-10	0.9
Scoliosis	M41	ICD-10	0.9
Dysphagia	R13	ICD-10	0.8
Dependence on enabling machines and devices	Z99	ICD-10	0.8
Agent resistant to penicillin and related antibiotics	U80	ICD-10	0.8

Osteoporosis with pathological fracture	M80	ICD-10	0.8
Other diseases of digestive system	K92	ICD-10	0.8
Cerebral Infarction	I63	ICD-10	0.8
Calculus of kidney and ureter	N20	ICD-10	0.7
Mental and behavioural disorders due to use of alcohol	F10	ICD-10	0.7
Other medical procedures as the cause of abnormal reaction of the patient	Y84	ICD-10	0.7
Abnormalities of heartbeat	R00	ICD-10	0.7
Unspecified acute lower respiratory infection	J22	ICD-10	0.7
Problems related to life-management difficulty	Z73	ICD-10	0.6
Other abnormal findings of blood chemistry	R79	ICD-10	0.6
Personal history of risk-factors, not elsewhere classified	Z91	ICD-10	0.5
Open wound of forearm	S51	ICD-10	0.5
Depressive episode	F32	ICD-10	0.5
Spinal stenosis (secondary code only)	M48	ICD-10	0.5
Disorders of mineral metabolism	E83	ICD-10	0.4
Polyarthrosis	M15	ICD-10	0.4
Other anaemias	D64	ICD-10	0.4
Other local infections of skin and subcutaneous tissue	L08	ICD-10	0.4
Nausea and vomiting	R11	ICD-10	0.3
Other noninfective gastroenteritis and colitis	K52	ICD-10	0.3
Fever of unknown origin	R50	ICD-10	0.1

Appendix 2. Paper in submission: Systematic Review of the Association of the Hospital Frailty Risk Score with Characteristics and Mortality in Patients with Cerebrovascular and Cardiovascular Disease.

Introduction:

Frailty is defined as a clinical syndrome characterised by the impairment of multiple organ systems, leading to increased vulnerability to stress and adverse outcomes such as institutionalisation and death [4]. Given the increasing age of the population, the population at risk of frailty is increasing [3].

Cardiovascular disease (CVD) is the largest cause of mortality and morbidity worldwide [183]. Frailty is co-existent in up to 60% of people with CVD and frailty is associated with a three-fold increased risk of mortality from CVD [20, 199]. The underlying mechanisms relating CVD and frailty are poorly understood, however is most likely linked to chronic inflammation, shared risk factors and comorbidity [3, 21, 115]. Frail patients admitted to hospital experience longer length of stays, higher total costs and increased likelihood of all-cause mortality.

There are a variety of tools available to stratify frailty in primary care and hospital settings [9-11, 86, 88]. The Hospital Frailty Risk Score (HFRS) was developed by *Gilbert et al.* and validated using an United Kingdom (UK) cohort. The HFRS quantifies frailty using a cumulative deficit model and is entirely derived from routinely collected health record data using 109 individually weighted International Classification of Diseases (ICD) – 10th edition codes. The HFRS has the benefit of being relatively less resource intensive for the assessment of frailty in comparison to other frailty assessment tools, due to the lack of requirement for clinical assessment. Studies using the HFRS are relatively few given its reliance on ICD codes; however its use has been validated in a variety of countries [10, 89-91].

The aim of this systematic review was to provide an overview of the use of the HFRS in describing the prevalence of frailty in patients with CVD, the clinical characteristics of frail patients with CVD, and the likelihood of mortality of frail patients with CVD.

Methods:

This systematic review was performed and reported in accordance with the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guidance [96] and the protocol pre-registered with the *International Prospective Register of Systematic Reviews* (PROSPERO, CRD42022371883) (**Fig. 1**). A total of 6 databases from inception until November 2022 were comprehensively searched: MEDLINE (EBSCO), EMBASE (Ovid), AMED (EBSCO), CINAHLPlus (EBSCO), AGELine (EBSCO) and Web of Science. The search strategy utilised both database subject headings and text word searching in the title and abstract using terms for "hospital frailty risk score" and "cardiovascular disease" (**Appendix 1**). One reviewer (BSS) performed the search.

Studies using the HFRS, investigating prevalence, clinical characteristics and/or outcomes of patients with CVD published in the English language were included. Study designs that were eligible for inclusion were randomised controlled trials, as well as retrospective and prospective observational cohort studies. There was no restriction on the time or the definition of CVD. Conference abstracts, research letters and review articles were excluded.

One reviewer (BSS) imported all references into Endnote and removed exact duplicates. The remaining references were imported into Rayyan. One reviewer (BSS) screened all titles and removed references that did not meet the inclusion criteria. Two reviewers (BSS and SPKM) screened abstracts and full texts independently to ensure no studies were incorrectly excluded. Any disagreements between the reviewers were resolved by a third reviewer (CW).

Two reviewers (BSS and SPKM) independently extracted data from full-text articles into pre-formed tables and any disagreements between the reviewers were resolved by a third reviewer (CW). The following data were extracted: study design, study year and country, number and age of the participants stratified by frailty status, the prevalence and clinical characteristics of the participants stratified by frailty status, and all-cause mortality stratified by frailty status.

The quality of each study was assessed independently by two reviewers (BSS and SPKM) using the *Newcastle-Ottawa Quality Assessment for Cohort Study* tool and any disagreements resolved by a third reviewer (CW) [97]. The tool assessed studies using 3 domains (selection, comparability, and outcome) each with multiple choice outcomes and a 'star' to represent quality. The selection domain assessed the representativeness of the cohort, cohort selection method, ascertainment of exposure and whether the exposure was present at the start of the study. The comparability domain assessed the quality of adjustment for confounders. The outcome domain assessed how the outcome was ascertained, length of follow-up, and adequacy of follow-up. Finally a grade of 'good quality' (3 or 4 stars in selection domain 1 or 2 stars in comparability domain and 2 or 3 stars in outcome domain), 'fair quality' (2 stars in selection domain, 1 or 2 stars in comparability domain and 2 or 3 stars in outcome domain) and 'poor quality' (0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome domain) was assigned.

Given the heterogeneity between each study, a meta-analysis was not conducted. The extracted data was compared descriptively. The narrative synthesis was developed and reported in accordance with the *Synthesis Without Meta-analysis* (SWiM) guidance and the *Cochrane Handbook* [99, 100]. Results were grouped according to the type of CVD investigated in each study.

Results:

A total of 10,341 unique references were identified, which after screening yielded 17 studies for inclusion in the final analysis and quality appraisal (**Figure 1)**. Of the 17 studies, all were retrospective cohort studies with 2 using propensity-score matching. Studies were conducted in Australia (N=9), US (N=4), Germany (N=2), Canada (N=1) and Korea (N=1). Across the 17 included studies, there was a total of 20,419,197 cases of CVD. Studies investigated heart failure (HF) (N=7), acute myocardial infarction (AMI) (N=4), stroke (N=4), atrial fibrillation

(AF) (N=1), cardiac arrest (N=1), and general CVD (N=1) which included primary hypertension, HF, AF, hypotension and chronic ischaemic heart disease.

There was varied reporting of each HFRS category. All studies described the prevalence of each HFRS category (N=17), whilst most studies described HFRS categories by age (N=10), clinical characteristics (N=10) and adjusted odds ratio (aOR) of mortality (N=13). Some studies classified a HFRS ≥ 5 as frail, hence combining the intermediate and high frailty groups (N= 6) and one study had a no risk (HFRS=0) category (N=1) (**Table 1**). All 17 studies were rated 'good' quality according to the Newcastle-Ottawa Quality Assessment for Cohort Study tools **(Figure 2 and Appendix 2)**.

The prevalence of low frailty risk ranged from 2.0% to 86.5%, compared to 12.4% to 68.3% for intermediate frailty risk and 1.6% to 40.9% for the high frailty risk group. The average age of the low HFRS group ranged from 62.2 to 83.6, compared 70.5 to 84.3 for the intermediate HFRS group and 75.1 to 84.6 for the high HFRS group. Increasing frailty score was generally associated with female sex and an increased prevalence of comorbidities, increased length of stay and increased odds of all-cause mortality.

One study investigated the impact of the HFRS on general CVD in patients aged over 75 years [19]. The prevalence of low frailty risk was 24.6%, intermediate frailty risk was 34.5% and high frailty risk was 40.9%. The average age of the low frailty risk group was 82.4 years, compared to 83.7 years for the intermediate frailty group and 84.1 years for the high frailty risk group. The high HFRS group were more likely to be female (54.6%), have a Charlson Comorbidity Index (CCI) above 2 (86.8%), and increased length of stay beyond 10 days (23.9%). This study reported specific diagnoses of AF, HF, primary hypertension, hypotension and chronic ischaemic heart disease. The age, prevalence and clinical characteristic of these cohorts were not described. In this study, bivariate analysis had a significantly high relation coefficient (0.92, $p<0.01$) and was reported over logistic regression as the regression results

were determined to be biased. There were no confidence intervals reported in this study. This study reported 30-day mortality for a combined intermediate/high frailty risk group. For the intermediate/high frailty risk group, odds of mortality was 1.73 for general CVD compared to the low frailty risk group. When stratified by diagnosis, the odds of 30-day all-cause mortality using bivariate analysis was 2.15 for primary hypertension, 2.31 for HF, 2.52 for AF, 2.65 for hypotension and 2.56 for chronic ischaemic heart disease compared to the low frailty risk group. (**Table 1**) [101].

Eight studies used the HFRS in a HF cohort [90, 91, 101-106]. The prevalence of low frailty risk ranged from 24.6% to 86.1%, intermediate frailty risk ranged from 12.4% to 47.4%, and high frailty risk ranged from 0.1% to 13.9%. The average age of HF patients at low risk ranged from 72.0 to 82.4, intermediate risk ranged from 76.0 to 80.5, and high frailty risk ranged from 81.0 to 82.7 years. Increasing HFRS category was mostly associated with an increased likelihood of female sex (1 study observed decreasing prevalence), a higher prevalence of cardiovascular and non-cardiovascular co-morbidities and CCI, and increased length of stay. The aOR of 30-day all-cause mortality ranged from 1.52 (95%CI [1.50-1.54]) to 2.80 (95%CI [2.70-2.90]) in patients at intermediate risk, and 1.60 (95%CI [1.35-1.90]) to 3.50 (95%CI [3.40-3.68]) for patients at high risk, compared to their low-risk counterparts (**Table 1**).

Four studies used the HFRS in an AMI cohort [89, 102, 107, 108]. The prevalence of low frailty risk ranged from 49.3% to 86.5%, intermediate frailty risk ranged from 13.4% to 36.8%, and high frailty risk ranged from 0.1% to 13.9%. The age of AMI patients at low risk ranged from 62.2 to 83.6 years, at intermediate risk ranged from 70.5 to 84.3 years, and high frailty risk ranged from 80.0 to 84.6 years. Increasing HFRS category was associated with increased likelihood of female sex, lower likelihood of being white, and a higher prevalence of cardiovascular and non-cardiovascular co-morbidities and CCI. The aOR of mortality ranged from 1.40 (95%CI [1.10-1.79]) to 4.02 (95%CI [3.91-4.13]) in patients at intermediate risk,

and 1.58 [(95%CI 1.12-2.24]) to 4.63 (95%CI [4.36-4.92]) for patients at high risk, compared to their low-risk counterparts (**Table 1**).

Four studies used the HFRS in the overall stroke cohort (stroke, TIA or intracerebral haemorrhage) [95, 109-111]. Not all studies reported every outcome. The prevalence of intermediate frailty risk ranged from 45.0% to 48.0%, and high frailty risk ranged from 22.0% to 27.0%. The age of stroke patients at intermediate risk ranged from 76.0 to 83.8 years, and high frailty risk ranged from 81.0 to 84.2 years. Increasing HFRS category was associated with an increased likelihood of female sex, increased prevalence of comorbidities and increased length of stay. Of the 2 studies that reported aOR of 30-day mortality, this ranged from 1.78 (95%CI [1.33-2.39]) to 2.08 (95%CI [1.62-2.67]) in patients at intermediate risk, and 1.34 (95%CI [1.03-1.75]) to 3.55 (95%CI [2.80-4.52]) for patients at high risk, in comparison to their low-risk counterparts. (**Table 1**).

Two studies used the HFRS in an AF cohort [101, 112]. Neither study described the age distribution or clinical characteristics in each HFRS category. One study reported non-valvular AF patients exclusively [113]. The prevalence of intermediate frailty risk in was 14.2% and high frailty risk was 1.6% [113]. This study did not report outcomes stratified by frailty risk category. The study of general CVD reported an aOR of 30-day mortality of 2.52 for combined intermediate/high frailty risk patients compared to their low frailty risk counterparts (**Table 1**) [101]. There was no CI reported for this result.

One study used the HFRS in a cardiac arrest cohort [114]. This study described frailty as HFRS ≥ 5, combining intermediate and high risk scores under this category. The prevalence of low frailty risk was 81.4% and intermediate or high frailty risk was 18.6%. This study did not describe the distribution of age, prevalence and clinical characteristics of each HFRS category. The odds of 30-day in-hospital mortality was 2.80 (95%CI [1.52-5.15]) for the intermediate/high frailty group, compared to the low-risk group (**Table 1**).

Discussion

Frailty is well-established in the literature as being a significant risk factor for increased hospital length of stay, total costs, adverse health outcomes and mortality [4]. Despite the abundance of literature investigating the impact of frailty on CVD outcomes, there is little data on the utility of the HFRS, completely derived from ICD-10 codes, in CVD cohorts. This is the first systematic review of the utility of the HFRS to investigate the prevalence of frailty in CVD patients, clinical characteristics of frail patients with CVD, and likelihood of mortality of frail patients with CVD. This study has several important findings. Firstly, intermediate, or high frailty risk as defined by the HFRS is present in a substantial proportion of patients across a range of CVD, with patients at increased frailty risk more likely to be older, female sex, non-white race, and have a higher prevalence of co-morbidities. Secondly, the HFRS shows significant association with mortality across most CVD. Finally, this review indicates that frailty is an important consideration in CVD patients as such patients are a great burden to health services by incurring a longer length of stay and higher total charges.

There are many validated tools to assess frailty, yet there is no consensus on which tool to use [117]. As developed countries transition to digital systems, there is increasing reliance on electronic health care records and automation of processes to ensure efficiency and optimisation of patient care [118]. The HFRS was derived entirely from routinely collected health record data using ICD codes and then validated on a UK cohort [10]. The HFRS has since been used with Australian, United States, and German CVD cohorts [89, 91, 110]. The performance of the HFRS is comparable to other digital health record frailty measures and other well-known measures such as the Frailty Index and Clinical Frailty Scale [10, 94]. However, most studies comparing tools do not investigate patients with CVD specifically.

The reported prevalence of frailty is highly variable in the literature as it is dependent on the frailty measure used [16]. A meta-analysis of 31,343 community-based participants estimated

the prevalence of frailty to be around 17.9%, however, none of the included studies used the HFRS [16]. This systematic review suggests the prevalence of frailty as defined by the HFRS in CVD ranges between 12.4-48.0% for intermediate risk, and 0.1-40.9% for high risk. Such a range in prevalence could be due to the specific CVD of interest or the criteria of cohort selection. Reported prevalence values seemingly remained constant across studies investigating the same CVD. However, studies vary in participant inclusion criteria. Most frailty studies have a minimum age cut-off of 65 or 75 years; yet this review found some studies also included all adult hospitalisation with no age restrictions [101]. As frailty is related to ageing, studies adopting age restrictions would have a larger proportion of patients at risk of frailty, rendering them less generalisable to the entire population [4, 6, 16].

The impact of frailty on outcomes varies with frailty measure, study setting and length of follow up [90]. Frailty has been shown to increase odds of CVD by 35% [22]. In turn, CVD increases the odds of frailty, demonstrating a bidirectional relationship [22]. The positive correlation is observed using most frailty measures including the HFRS which performs as well as most frailty and comorbidity tools as determined by area under receiver operating curves [10, 92, 94]. There are multiple underlying mechanisms linking CVD and frailty. In summary, both frailty and CVD are age-related conditions causing a pro-inflammatory state, with increased levels of pro-inflammatory cytokines and immune markers such as interleukin 6 and C-reactive protein [115]. Increased inflammation perpetuates a cycle of frailty, driving sarcopenia and leading to adverse health outcomes [80]. In the context of CVD, the presence of inflammation drives atherosclerosis and plaque instability, leading to increased likelihood of plaque rupture and associated complications [73]. Therefore, CVD and frailty drive one another and are major public health priorities [116].

In this systematic review, increasing HFRS category was associated with increased odds of all-cause mortality across all CVD. This supports previous literature corroborating frailty, as

defined by most other measures, associated with an increase in the odds of all-cause mortality from CVD [16, 22, 115, 116]. In the pilot study where non-CVD specific cohorts were used, receiver operating curves for the HFRS predicting 30-day mortality, long hospital stay, and 30-day readmission was 0.60, 0.68 and 0.56 respectively with the performance of the categorised HFRS fairly overlapping with the Frailty Phenotype and Frailty Index scales, and the continuous HFRS demonstrating moderate agreement with Rockwood's Frailty Index [10]. Studies using the HFRS in non-CVD specific cohorts also demonstrate an increased odds of mortality with increasing HFRS, with some studies comparing the HFRS to other frailty measures demonstrating comparable performance [124, 125].

This study found the increasing HFRS was mostly associated with female sex, non-white race, and increased prevalence of comorbidities. Most measures of frailty demonstrate increased prevalence of frailty in females, patients from non-white racial groups and patients with multimorbidity [5, 7, 78]. There are a variety of factors implicated in this relationship. Women are more likely to have a higher percentage body composition of fat and are more affected by biological and socio-economic factors of frailty [119, 120]. Non-white race may be a factor in the development of frailty, even after adjustment for age, sex and socio-economic status, however the mechanisms behind this are poorly understood, with conflicting results between studies [121, 122]. Many studies corroborate increasing frailty with increasing comorbidity burden. Whilst both overlap, both have two distinct process, both related to age [123]. The normal physiological process of ageing, and it's interaction with diseases leads to the development of frailty [123]. Comorbidities play a distinct role in introducing the ageing patient to acute stressors, leading to rapid decline in functional abilities in a frail patient [123]. As the HFRS was formed as a cumulative deficit model of over 109 comorbidities ranging from dementia to infection, patients with increased HFRS are inherently more likely to also have more comorbidities [10].

The clinical implications of this study may be substantial given the increasing age and frailty of the population, the increasing prevalence of CVD, and the drive to digital systems in certain areas of the world that facilitate electronic health record data [6, 17, 126]. The drive toward such systems prompts the utility of automated systems to improve efficiency, increase accuracy and identify needs of at-risk individuals based on their past medical history and risk factors [100]. Frailty is a reversible condition and progression can be mediated by earlier identification, assessment, and intervention by cardiologists to improve prognosis in CVD, though the possible outcomes of intervention have not been explored [9, 30, 117]. However, medications used to treat cardiovascular conditions may be contra-indicated in the frail elderly on the basis of risk-benefit assessment [127].

This systematic review has several strengths. Firstly, there was a systematic approach to identifying research articles guided by PRISMA guidelines, ensuring optimal identification of potential articles and minimisation of bias. Each abstract and full text was screened by two reviewers, with conflicts resolved by a third, independent reviewer. Secondly, the search strategy was comprehensive through the inclusion of all synonyms for each search term, verified by experts in cardiology, epidemiology and systematic reviews. This allowed for inclusion of most papers on the topic of CVD and frailty, allowing authors to specifically screen for the studies that included the HFRS. Thirdly, all major databases were searched. MEDLINE, EMBASE and WOS are among the largest repositories for peer-reviewed research. This reassures the search for articles was comprehensive.

This systematic review has several limitations. There was a large degree of heterogeneity between the study focus, study design and reporting of studies. Most studies reported mortality in the intermediate and high HFRS groups separately, whereas others combined both groups. For adjusted analysis, most studies used a low HFRS category as the reference group, but there were some studies that derived another cohort with a HFRS of 0 and used this cohort as the

reference group. Additionally, studies used different covariates for the multivariable analyses. Not all studies described the prevalence or clinical characteristics of each HFRS cohorts. Furthermore, all studies in this review were from countries that have made the transition to electronic health record keeping and hold registries. Therefore, this review cannot be generalised to healthcare systems that cannot utilise the ICD coding system or digital systems in general.

In conclusion, this systematic review suggests that the HFRS, formed entirely from ICD-10 codes, identifies a high risk phenotype that is associated with mortality in patients with CVD. Increased HFRS is associated with increased age, female sex, non-white racial groups and increased odds of 30-day all-cause mortality amongst most admission CVD diagnoses. As the burden of frailty and CVD increases and healthcare records transition electronically, the HFRS proves to be an efficient and effective tool to stratify frailty risk. Early identification of frailty risk using the HFRS may allow healthcare professionals to optimise cardiovascular risk factors and prevent the downstream adverse outcomes of frailty. Some research suggests that the HFRS performs comparably to other frailty measures in predicting adverse outcomes. Future work should assess the performance of HFRS in comparison to other contemporary measures of frailty in CVD cohorts in identifying high risk patients.

Appendix 3. MEDLINE via EBSCO search strategy.

Search	Query	Results
S1	MH Cardiovascular diseases+	2,654,667
S2	MH Cerebrovascular disorders+	415,585
S3	MH Peripheral vascular diseases+	57,271
S4	MH Heart disease risk factors+	4,949
S5	MH Pulmonary embolism+	42,580
S6	TI CVD OR AB CVD	47,631
S7	TI (((Coronary OR Cardiovascular OR Ischaem* OR Ischem* OR Heart OR Myocard* OR Cerebrovascular OR peripheral) N2 (Disease* OR condition* OR disorder*))) OR AB (((Coronary OR Cardiovascular OR Ischaem* OR Ischem* OR Heart OR Myocard* OR Cerebrovascular OR peripheral) N2 (Disease*)	571,081
S8	TI Atherosclero* OR AB Atherosclero*	166,821
S9	TI Arrythmia* OR AB Arrythmia*	924
S10	TI (((Atrial OR Venric*) N2 (Flutter* or Fib*))) OR AB (((Atrial OR Venric*) N2 (Flutter* or Fib*)))	88,985
S11	TI Arterio* OR AB Arterio*	135,877
S12	TI (((Heart* OR cardiac* OR myocard*) N2 (failure OR insufficien*))) OR AB (((Heart* OR cardiac* OR myocard*) N2 (failure OR insufficien*)))	218,221
S13	TI CCF OR AB CCF	2,046
S14	TI CHF OR AB CHF	15,455
S15	TI (((myocard* OR heart* OR cardiac*) N2 (infarct* OR attack* OR arrest* OR sudden))) OR AB (((myocard* OR heart* OR cardiac*) N2 (infarct* OR attack* OR arrest* OR sudden)))	281,950
S16	TI IHD OR AB IHD	6,532
S17	TI (Cerebrovascular N2 (incident* OR accident*)) OR AB (Cerebrovascular N2 (incident* OR accident*))	7,898
S18	TI CVA OR AB CVA	3,301
S19	TI CVI OR AB CVI	3,386
S20	TI (((Pulm* OR Venous OR Vein OR Art*) N2 (Embol* OR Thromb*))) OR AB (((Pulm* OR Venous OR Vein OR Art*) N2 (Embol* OR Thromb*)))	163,207
S21	TI Claudica* OR AB Claudica*	11,703
S22	TI (((Peripheral OR Limb OR Vascular) N2 (Ischaem* OR Ischem*))) OR AB (((Peripheral OR Limb OR Vascular) N2 (Ischaem* OR Ischem*)))	19,914
S23	TI Stroke* OR AB Stroke*	295,706
S24	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23	3,149,197
S25	MM Frailty	6,817
S26	AB Frail* OR TI Frail*	30,965
S27	AB “HFRS” OR TI “HFRS”	1,558
S28	AB HFRS OR TI HFRS	2,594
S29	AB Gilbert* N2 Score OR TI Gilbert* N2 Score	28
S30	S25 OR S26 OR S27 OR S28 OR S29	33,796

S31	MH Animals+	25,862,539
S32	MH Humans	20,806,911
S33	S31 NOT S32	5,055,637
S34	S24 AND S30	5,281
S35	S34 NOT S33	5,241

Appendix 4. EMBASE via EBSCO search strategy.

Search	Query	Results
S1	Cardiovascular disease.sh.	320,495
S2	Cerebrovascular disease.sh.	64,373
S3	Peripheral vascular disease.sh.	24,071
S4	Pulmonary embolism.sh.	520
S5	CVD.ab. or CVD.ti.	71,302
S6	((Coronary or Cardiovascular or Ischaem* or Ischem* or Heart or Myocard* or Cerebrovascular or peripheral) adj2 (Disease* or condiMon* or disorder*)). ab. or ((Coronary or Cardiovascular or Ischaem* or Ischem* or Heart or Myocard* or Cerebrovascular or peripheral) adj2 (Disease* or condiMon* or disorder*)).ti.	781,524
S7	Atherosclero*. ab. or Atherosclero*.ti.	231,281
S8	Arrythmia*. ab. or Arrythmia*.ti.	2,312
S9	((Atrial or Venric*) adj2 (Flutter* or Fib*)). ab. or ((Atrial or Venric*) adj2 (Flutter* or Fib*)).ti.	157,831
S10	Arterio*. ab. or Arterio*.ti.	164,100
S11	((Heart* or cardiac* or myocard*) adj2 (failure or insufficien*)). ab. or ((Heart* or cardiac* or myocard*) adj2 (failure or insufficien*)).M.	351,630
S12	CCF.ab. or CCF.ti.	2,992
S13	CHF.ab. or CHF.ti.	29,241
S14	((myocard* or heart* or cardiac*) adj2 (infarct* or attack* or arrest* or sudden)). ab. or ((myocard* or heart* or cardiac*) adj2 (infarct* or attack* or arrest* or sudden)).ti.	407,141
S15	IHD.ab. or IHD.ti.	10,558
S16	(Cerebrovascular adj2 (incident* or accident*)). ab. or (Cerebrovascular adj2 (incident* or accident*)).ti.	12,383
S17	CVA.ab. or CVA.ti.	7,627
S18	CVI.ab. or CVI.ti.	4,862
S19	((Pulm* or Venous or Vein or Art*) adj2 (Embol* or Thromb*)). ab. or ((Pulm* or Venous or Vein or Art*) adj2 (Embol* or Thromb*)).ti.	231,466
S20	Claudica*. ab. or Claudica*.ti.	16,243
S21	((Peripheral or Limb or Vascular) adj2 (Ischaem* or Ischem*)). ab. or ((Peripheral or Limb or Vascular) adj2 (Ischaem* or Ischem*)).ti.	24,808
S22	Stroke*. ab. or Stroke*. M.	470,926
S23	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	2,383,521
S24	Frailty.sh.	22,020
S25	Frail*. ab. or Frail*.ti.	47,608
S26	HFRS.ab. or HFRS.ti.	1,815
S27	((Gilbert* adj2 Score). ab. or Gilbert*.mp.) adj2 Score.ti.	1
S28	24 or 25 or 26 or 27	52,275
S29	23 and 28	8,271

Appendix 5. AMED via EBSCO search strategy.

Search	Query	Results
S1	TI CVD OR AB CVD	211
S2	TI (((Coronary OR Cardiovascular OR Ischaem* OR Ischem* OR Heart OR Myocard* OR Cerebrovascular OR peripheral) N2 (Disease* OR condition* OR disorder*))) OR AB (((Coronary OR Cardiovascular OR Ischaem* OR Ischem* OR Heart OR Myocard* OR Cerebrovascular OR peripheral) N2 (Disease* OR condition* OR disorder*)))	3,666
S3	TI Atherosclero* OR AB Atherosclero*	591
S4	TI Arrythmia* OR AB Arrythmia*	6
S5	TI (((Atrial OR Venric*) N2 (Flutter* or Fib*))) OR AB (((Atrial OR Venric*) N2 (Flutter* or Fib*)))	114
S6	TI Arterio* OR AB Arterio*	251
S7	TI (((Heart* OR cardiac* OR myocard*) N2 (failure OR insufficien*))) OR AB (((Heart* OR cardiac* OR myocard*) N2 (failure OR insufficien*)))	995
S8	TI CCF OR AB CCF	16
S9	TI CHF OR AB CHF	147
S10	TI (((myocard* OR heart* OR cardiac*) N2 (infarct* OR attack* OR arrest* OR sudden))) OR AB (((myocard* OR heart* OR cardiac*) N2 (infarct* OR attack* OR arrest* OR sudden)))	910
S11	TI IHD OR AB IHD	21
S12	TI (Cerebrovascular N2 (incident* OR accident*)) OR AB (Cerebrovascular N2 (incident* OR accident*))	268
S13	TI CVA OR AB CVA	167
S14	TI CVI OR AB CVI	26
S15	TI (((Pulm* OR Venous OR Vein OR Art*) N2 (Embol* OR Thromb*))) OR AB (((Pulm* OR Venous OR Vein OR Art*) N2 (Embol* OR Thromb*)))	486
S16	TI Claudica* OR AB Claudica*	166
S17	TI (((Peripheral OR Limb OR Vascular) N2 (Ischaem* OR Ischem*))) OR AB (((Peripheral OR Limb OR Vascular) N2 (Ischaem* OR Ischem*)))	82
S18	TI Stroke* OR AB Stroke*	9,787
S19	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18	15,913
S20	TI Frail* OR AB Frail*	722
S21	TI “HFRS” OR AB “HFRS”	0
S22	TI HFRS OR AB HFRS	4
S23	TI Gilbert* N2 Score AB Gilbert* N2 Score	0
S24	S20 OR S21 OR S22 OR S23	726
S25	S19 AND S24	43

Appendix 6. CINAHLPlus via EBSCO strategy.

Search	Query	Results
S1	MH Cardiovascular diseases+	671,466
S2	MH Cerebrovascular disorders+	124,887
S3	MH Peripheral vascular diseases+	19,821
S4	MH Heart disease risk factors+	0
S5	MH Pulmonary embolism+	10,961
S6	TI CVD OR AB CVD	15,614
S7	TI (((Coronary OR Cardiovascular OR Ischaem* OR Ischem* OR Heart OR Myocard* OR Cerebrovascular OR peripheral) N2 (Disease* OR condition* OR disorder*))) OR AB (((Coronary OR Cardiovascular OR Ischaem* OR Ischem* OR Heart OR Myocard* OR Cerebrovascular OR peripheral) N2 (Disease*	150,417
S8	TI Atherosclero* OR AB Atherosclero*	29,485
S9	TI Arrythmia* OR AB Arrythmia*	177
S10	TI (((Atrial OR Venric*) N2 (Flutter* or Fib*))) OR AB (((Atrial OR Venric*) N2 (Flutter* or Fib*)))	35,805
S11	TI Arterio* OR AB Arterio*	15,885
S12	TI (((Heart* OR cardiac* OR myocard*) N2 (failure OR insufficien*))) OR AB (((Heart* OR cardiac* OR myocard*) N2 (failure OR insufficien*)))	65,092
S13	TI CCF OR AB CCF	307
S14	TI CHF OR AB CHF	4,164
S15	TI (((myocard* OR heart* OR cardiac*) N2 (infarct* OR attack* OR arrest* OR sudden))) OR AB (((myocard* OR heart* OR cardiac*) N2 (infarct* OR attack* OR arrest* OR sudden)))	79,430
S16	TI IHD OR AB IHD	1,238
S17	TI (Cerebrovascular N2 (incident* OR accident*)) OR AB (Cerebrovascular N2 (incident* OR accident*))	2,178
S18	TI CVA OR AB CVA	1,062
S19	TI CVI OR AB CVI	1,326
S20	TI (((Pulm* OR Venous OR Vein OR Art*) N2 (Embol* OR Thromb*))) OR AB (((Pulm* OR Venous OR Vein OR Art*) N2 (Embol* OR Thromb*)))	38.936
S21	TI Claudica* OR AB Claudica*	2,328
S22	TI (((Peripheral OR Limb OR Vascular) N2 (Ischaem* OR Ischem*))) OR AB (((Peripheral OR Limb OR Vascular) N2 (Ischaem* OR Ischem*)))	3,691
S23	TI Stroke* OR AB Stroke*	112,028
S24	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23	810,510
S25	MM Frailty	0
S26	AB Frail* OR TI Frail*	17,177
S27	AB “HFRS” OR TI “HFRS”	152
S28	AB HFRS OR TI HFRS	232
S29	AB Gilbert* N2 Score OR TI Gilbert* N2 Score	10
S30	S25 OR S26 OR S27	17,379

	OR S28 OR S29	
S31	MH Animals+	104,767
S32	MH Humans	2,620,373
S33	S31 NOT S32	95,315
S34	S24 AND S30	2,121
S35	S34 NOT S33	2,113

Appendix 7. AgeLine via EBSCO search strategy.

Search	Query	Results
S1	AB CVD OR TI CVD	366
S2	AB (((Coronary OR Cardiovascular OR Ischaem* OR Ischem* OR Heart OR Myocard* OR Cerebrovascular OR peripheral) N2 (Disease* OR condition* OR disorder*))) OR TI (((Coronary OR Cardiovascular OR Ischaem* OR Ischem* OR Heart OR Myocard* OR Cerebrovascular OR peripheral) N2 (Disease* OR condition* OR disorder*)))	4,109
S3	AB Atherosclero* OR TI Atherosclero*	351
S4	AB Arrythmia* OR TI Arrythmia*	0
S5	AB (((Atrial OR Venric*) N2 (Flutter* or Fib*))) OR TI (((Atrial OR Venric*) N2 (Flutter* or Fib*)))	398
S6	AB Arterio* OR TI Arterio*	117
S7	AB (((Heart* OR cardiac* OR myocard*) N2 (failure OR insufficien*))) OR TI (((Heart* OR cardiac* OR myocard*) N2 (failure OR insufficien*)))	1,351
S8	AB CCF OR TI CCF	6
S9	AB CHF OR TI CHF	156
S10	AB (((myocard* OR heart* OR cardiac*) N2 (infarct* OR attack* OR arrest* OR sudden))) OR TI (((myocard* OR heart* OR cardiac*) N2 (infarct* OR attack* OR arrest* OR sudden)))	1,076
S11	AB IHD OR TI IHD	26
S12	AB (Cerebrovascular N2 (incident* OR accident*)) OR TI (Cerebrovascular N2 (incident* OR accident*))	106
S13	AB CVA OR TI CVA	33
S14	AB CVI OR TI CVI	17
S15	AB (((Pulm* OR Venous OR Vein OR Art*) N2 (Embol* OR Thromb*))) OR TI (((Pulm* OR Venous OR Vein OR Art*) N2 (Embol* OR Thromb*)))	165
S16	AB Claudica* OR TI Claudica*	32
S17	AB (((Peripheral OR Limb OR Vascular) N2 (Ischaem* OR Ischem*))) OR TI (((Peripheral OR Limb OR Vascular) N2 (Ischaem* OR Ischem*)))	51
S18	AB Stroke* OR TI Stroke*	3,555
S19	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18	8,836
S20	AB Frail* OR TI Frail*	6,047
S21	AB “HFRS” OR TI “HFRS”	11
S22	AB HFRS OR TI HFRS	15
S23	AB Gilbert* N2 Score OR TI Gilbert* N2 Score	0
S24	S20 OR S21 OR S22 OR S23	6,051
S25	S19 AND S24	400

Appendix 8. Web of Science search strategy.

Search	Query	Results
S1	(TI=(CVD)) OR AB=(CVD)	79,963
S2	(TI= (((Coronary OR Cardiovascular OR Ischaem* OR Ischem* OR Heart OR Myocard* OR Cerebrovascular OR peripheral) NEAR/3 (Disease* OR condition* OR disorder*)))) OR AB= (((Coronary OR Cardiovascular OR Ischaem* OR Ischem* OR Heart OR Myocard* OR Cerebrovascular OR peripheral) NEAR/3 (Disease* OR condition* OR disorder*)))	559,607
S3	(TI=(Atherosclero*)) OR AB=(Atherosclero*)	170,168
S4	(TI=(Arrythmia*)) OR AB=(Arrythmia*)	922
S5	(TI=(Arterio*)) OR AB=(Arterio*)	103,870
S6	(TI= (((Atrial OR Venric*) NEAR/3 (Flutter* or Fib*)))) OR AB= (((Atrial OR Venric*) NEAR/3 (Flutter* or Fib*)))	101,023
S7	(TI= (((Heart* OR cardiac* OR myocard*) NEAR/3 (failure OR insufficien*)))) OR AB= (((Heart* OR cardiac* OR myocard*) NEAR/3 (failure OR insufficien*)))	23,5865
S8	(TI=(CCF)) OR AB=(CCF)	3,737
S9	(TI=(CHF)) OR AB=(CHF)	18,160
S10	(AB= (((myocard* OR heart* OR cardiac*) NEAR/3 (infarct* OR attack* OR arrest* OR sudden)))) OR TI= (((myocard* OR heart* OR cardiac*) NEAR/3 (infarct* OR attack* OR arrest* OR sudden)))	280,921
S11	(TI= (IHD)) OR AB= (IHD)	5,383
S12	(AB= (Cerebrovascular NEAR/3 (incident* OR accident*))) OR TI= (Cerebrovascular NEAR/3 (incident* OR accident*))	6,265
S13	(TI=(CVA)) OR AB=(CVA)	4,046
S14	(TI=(CVI)) OR AB=(CVI)	5,488
S15	(AB= (((Pulm* OR Venous OR Vein OR Art*) NEAR/3 (Embol* OR Thromb*)))) OR AB= (((Pulm* OR Venous OR Vein OR Art*) NEAR/3 (Embol* OR Thromb*)))	109,731
S16	(AB=(Claudica*)) OR AB=(Claudica*)	7,843
S17	(AB= (((Peripheral OR Limb OR Vascular) NEAR/3 (Ischaem* OR Ischem*)))) OR AB=(((Peripheral OR Limb OR Vascular) NEAR/3 (Ischaem* OR Ischem*)))	16,687
S18	(AB=(Stroke*)) OR TI=(Stroke*)	350,533
S19	#18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1	1,642,104
S20	(TI=(Frail*)) OR AB=(Frail*)	36,408
S21	(AB=(“HFRS”)) OR TI=(“HFRS”)	1,337
S22	(AB=(HFRS)) OR TI=(HFRS)	1,337
S23	(TI= (Gilbert* NEAR/3 Score)) OR AB=(Gilbert* NEAR/3 Score)	44
S24	#23 OR #22 OR #21 OR #20	37,720
S25	#24 AND #19	3,915

Appendix 9. Data elements of the National Emergency Department Sample relevant to the dataset period, from HCUP.

Data Title	Years
Age in years at admission	2006-2020
Admission month	2006-2020
Admission day is on a weekend	2006-2020
Elixhauser Comorbidity Measure Refined for ICD-10-CM diagnosis codes	2019-2020
Version of the Elixhauser Comorbidity Measure Refined for ICD-10-CM diagnosis codes	2019-2020
Clinical Classifications Software (CCS): services and procedures classification	2008-2020
CPT-4/HCPCS procedures	2006-2020
Died in the ED, died in the hospital, or did not die	2006-2020
Weight to discharges in the universe	2006-2020
Disposition from ED	2006-2020
Disposition from inpatient discharge record	2006-2020
Discharge quarter	2006-2020
DRG in use on discharge date	2006-2020
DRG in use on discharge date, calculated without POA	2008-2020
DRG or MS-DRG grouper version used on discharge date	2006-2020
Clinical Classifications Software Refined (CCSR): ICD-10-CM Diagnosis Classification within Body System AAA	2018-2020
Default Clinical Classifications Software Refined (CCSR) for principal/first-listed ICD-10-CM diagnosis	2018-2020
Version of the Clinical Classifications Software Refined (CCSR) for ICD-10-CM diagnosis codes	2018-2020
Type of ED event	2006-2020
Indicator of sex	2006-2020
Source of HCUP Record (SID or SEDD)	2006-2020
Control/ownership of hospital	2006-2020
HCUP ED hospital identifier	2006-2020
Region of hospital	2006-2020
Hospital trauma level designation	2006-2020
Teaching status of hospital	2006-2020
Hospital urban-rural designation	2006-2020
Weight to hospitals in the universe	2006-2020
ICD-10-CM Diagnosis	2015-2020
ICD-10-CM External Cause of Morbidity Code	2015-2016
Injury ICD-10-CM diagnosis reported on record	2017-2020
Mechanism of injury: cut or pierce	2018-2020
Mechanism of injury: drowning or submersion	2018-2020
Mechanism of injury: fall	2018-2020
Mechanism of injury: fire, flame, hot object, or hot substance	2018-2020
Mechanism of injury: firearm	2018-2020

Mechanism of injury: machinery	2018-2020
Mechanism of injury: motor vehicle traffic, including the occupant of a car, motorcyclist, pedal cyclist, pedestrian, other, or unspecified	2018-2020
Mechanism of injury: natural or environmental, including venomous and nonvenomous bites and stings	2018-2020
Mechanism of injury: overexertion	2018-2020
Mechanism of injury: poisoning, including drugs and nondrugs	2018-2020
Mechanism of injury struck by or against	2018-2020
Mechanism of injury: suffocation	2018-2020
Intent of injury: assault	2018-2020
Intent of injury: intentional self-harm	2018-2020
Intent of injury: unintentional	2018-2020
Multiple ICD-10-CM injuries reported on record	2017-2020
Number of ICD-10-CM diagnoses on this discharge	2015-2020
Number of ICD-10-CM External Cause of Morbidity codes on this record	2015-2016
Number of procedures on the ED admission record	2015-2020
ICD-10-PCS procedure code	2015-2020
HCUP NEDS record identifier	2006-2020
Length of stay for inpatient stay	2006-2020
MDC in effect on discharge date	2006-2020
MDC in use on discharge date, calculated without POA	2009-2020
Number of universe discharges in the stratum	2006-2020
Number of universe hospitals in the stratum	2006-2020
Number of CPT/HCPCS procedures for this discharge	2006-2020
Stratum used to sample hospital	2006-2020
Expected primary payer, uniform	2006-2020
Expected secondary payer, uniform	2006-2020
Procedure Classes Refined for ICD-10-PCS procedure codes	2019-2020
Version of the Procedure Classes Refined for ICD-10-PCS procedure codes	2019-2020
Patient Location: NCHS Urban-Rural Code	2013-2020
Clinical Classifications Software Refined (CCSR): ICD-10-PCS Procedure Classification within Clinical Domain aaa	2019-2020
Version of the Clinical Classifications Software Refined (CCSR) for ICD-10-PCS procedure codes	2019-2020
Race/ethnicity of patient	2019-2020
Number of discharges in the sample for the stratum	2006-2020
Number of hospitals in the sample for the stratum	2006-2020
Total number of ED visits from this hospital in the NEDS	2006-2020
Total charge for ED services	2006-2020
Total charge for ED and inpatient services	2006-2020
Calendar year	2006-2020
Median household income for patient's ZIP Code (based on current year)	2006-2020

Appendix 10. Data elements of the National Inpatient Sample relevant to the dataset period, from HCUP.

Data Title	Years
Age in years at admission	1988-2020
Neonatal age (first 28 days after birth) indicator	2012-2020
Admission month	1988-2020
All Patient Refined DRG	2002-2020
All Patient Refined DRG: Risk of Mortality Subclass	2002-2020
All Patient Refined DRG: Severity of Illness Subclass	2002-2020
Admission day is on a weekend	1998-2020
Elixhauser Comorbidity Measure Refined for ICD-10-CM diagnosis codes	2019-2020
Version of the Elixhauser Comorbidity Measure Refined for ICD-10-CM diagnosis codes	2019-2020
Died during hospitalisation	1988-2020
Weight to discharges in the universe	1998-2020
Disposition of patient, uniform coding	1998-2020
Discharge quarter	1988-2020
Discharge quarter, as received from data source	2006-2011
DRG in use on discharge date	1988-2020
DRG in use on discharge date, calculated without POA	2008-2020
DRG or MS-DRG grouper version used on discharge date	1988-2020
Disease Staging: Principal Disease Category	2002-2010
Default Clinical Classifications Software Refined (CCSR) for principal/first-listed ICD-10-CM diagnosis	2018-2020
Version of the Clinical Classifications Software Refined (CCSR) for ICD-10-CM diagnosis codes	2018-2020
Clinical Classifications Software Refined (CCSR): ICD-10-CM Diagnosis Classification within Body System AAA	2018-2020
Diagnosis codes ICD version indicator	2015-2017
Diagnosis validity flag: Diagnosis n	1988-1997
Elective versus non-elective admission	2002-2020
Indicator of sex	1998-2020
Control/ownership of hospital	2008-2020
HCUP indicator of emergency department record	2007-2020
Bed size of hospital	1998-2020
Control/ownership of hospital	1998-2011
Census Division of hospital (STRATA)	2012-2020
Location/teaching status of hospital	1998-2020
NIS hospital number	2012-2020
Region of hospital	1998-2020
ICD-10-CM Birth Indicator	2019-2020
ICD-10-CM Delivery Indicator	2019-2020
ICD-10-CM Diagnosis	2015 Q4, 2016-2020
ICD-10-CM External Cause of Morbidity Code	2015 Q4, 2016
Injury ICD-10-CM diagnosis reported on record	2019-2020
Multiple ICD-10-CM injuries reported on record	2019-2020
Number of ICD-10-CM diagnoses on this discharge	2015 Q4, 2016-2020

Number of ICD-10-CM External Cause of Morbidity codes on this record	2015 Q4, 2016
Number of ICD-10-PCS procedures on this discharge	2015 Q4, 2016-2020
ICD-10-PCS Procedure	2015 Q4, 2016-2020
Service line based on ICD-10-CM/PCS codes	2019-2020
NIS record number	2012-2020
Length of stay, cleaned	1988-2020
MDC in effect on discharge date	1988-2020
MDC in use on discharge date, calculated without POA	2009-2020
Number of universe discharges in the stratum	1988-2020
Number of universe hospitals in the stratum	1988-2020
Stratum used to post-stratify hospital	1998-2020
Expected primary payer, uniform	1988-2020
Procedure Classes Refined for ICD-10-PCS procedure codes	2005-2015 Q3; 2019-2020
Major operating room ICD-10-PCS procedure indicator	2019-2020
Version of the Procedure Classes Refined for ICD-10-PCS procedure codes	2019-2020
Patient Location: NCHS Urban-Rural Code	2013-2020
Clinical Classifications Software Refined (CCSR): ICD-10-PCS Procedure Classification within Clinical Domain aaa	2019-2020
Version of the Clinical Classifications Software Refined (CCSR) for ICD-10-PCS procedure codes	2019-2020
Number of days from admission to procedure n	1988-2020
Procedure codes ICD version indicator	2015-2017
Race/ethnicity of patient	1988-2020
Number of discharges in the sample for the stratum	1988-2020
Number of hospitals in the sample for the stratum	1988-2020
Synthetic primary surgeon number	1988-2000
Number of hospital discharges in the sample	1998-2020
Total charges, cleaned	1988-2020
Indicator of a transfer into the hospital	2008-2020
Transfer out indicator	2010-2020
Calendar year	1988-2020
Median household income for patient's ZIP Code (based on current year)	2003-2020

Abbreviations: ICD-10-CM – International Classification of Diseases-Tenth Edition-Clinical Modification; ICD-10-PCS – International Classification of Diseases-Tenth Edition-Procedure Coding System.

Appendix 11. Paper in submission: A Retrospective Cohort Study about the Impact of Frailty on Emergency Department Encounters for Cardiovascular Disease:.

Introduction

Frailty is a clinical syndrome with impairment of multiple organ systems, leading to an increased vulnerability to stress, and is associated with an increased likelihood of adverse outcomes across a broad range of clinical conditions [4]. The elderly population is growing, and with it, the proportion of individuals living with frailty [3]. Frail patients have a greater burden of cardiovascular disease (CVD) [13, 115] exhibiting a bidirectional relationship; CVD is associated with a three-fold increase in frailty, while frailty is independently associated with increased mortality from CVD [16].

Different mechanisms link CVD and frailty, including chronic inflammation, common risk factors and increased comorbidities [3, 21, 115]. Several studies have described the association between CVD and frailty in the hospital inpatient setting [90, 102, 200]. However, there remains little data on whether the type of CVD encounter varies by frailty status in the Emergency Department (ED) setting. The outcomes of a patient presentation to the ED vary: some presentations are resolved within the ED, including on-site treatment and discharge; others are admitted for specialist inpatient hospital care; whilst others may result in death during the encounter. Therefore, utilising data derived from inpatient hospital episodes alone may not provide a full picture on the patterns of CVD encounters in secondary care amongst patients with different frailty burden and their associated outcomes. It is important to gain insight into patterns of acute CVD presentations amongst frail patients in the ED, as this would allow ED services to meet the needs of the growing frail population.

Therefore, the aim of this study was to describe the relationship between frailty status on the prevalence, clinical characteristics, causes, and outcomes of patients attending the ED with CVD using a national dataset.

Methods:

The National ED Sample (NEDS) was developed by the Healthcare Cost and Utilization Project sponsored by the Agency for Healthcare Research and Quality[201]. The NEDS provides accurate estimates of all hospital-owned ED encounters in the United States (US). This includes 989 hospitals located in 40 states amounting to approximately 145 million ED encounters. Patients demographics, outcomes, and comorbidities are all captured using International Classification of Diseases, Tenth Revision (ICD-10) codes [201].

The Hospital Frailty Risk Score (HFRS) was developed by Gilbert et al. to assess the risk of adverse outcomes in elderly patients using routinely collected healthcare data [10]. A cohort of elderly patients admitted for diagnoses associated with frailty was identified using ICD-10 codes [10]. The HFRS was created using ICD-10 codes to group patients into low risk (HFRS <5), intermediate risk (HFRS 5-15) and high risk (HFRS >15) [10]. The HFRS was validated using a local and national cohort in the United Kingdom [10]. Each component of the HFRS and the associated weighting is outlined in **Appendix 1**.

The ICD-10 codes were used to identify all adult discharge records with a principal diagnosis of an acute CVD encounters between 2016 and 2018 (**Supplementary Table 1**). This sample was filtered using ICD-10 codes into 7 selected CVD groups: acute myocardial infarction (AMI), atrial fibrillation (AF), ischaemic stroke, heart failure (HF), pulmonary embolism (PE), cardiac arrest and haemorrhagic stroke. The sample was then stratified according to their frailty status measured by the HFRS into 3 groups: low risk (HFRS <5), intermediate risk (HFRS 5 to 15) and high risk (HFRS >15) as defined by Gilbert et al [10].

The outcomes of this study were first, to calculate the proportion of encounters stratified by HFRS category (low, intermediate, and high), secondly, to examine discharge disposition (admission, discharge, mortality), stratified by CVD diagnosis and HFRS category, and finally, to determine the association between frailty, CVD and all-cause mortality in the ED.

Cases were excluded due to missing data for the following variables: age, sex, elective admission, ED mortality, primary expected payer, total ED and in-hospital charges and length of stay (n=40,341 [0.19%]). As this is an observational study, it was appraised according to the *Strengthening The Reporting of OBservational Studies in Epidemiology* (STROBE) recommendations (**Appendix 2**) [176].

Continuous variables including age, length of stay and total charges were summarised using median and interquartile ranges (IQR). Categorical variables were compared using the Chi-squared (X^2) test and summarised as percentages (%). Multivariable logistic regression was performed to determine the adjusted odds ratios (aOR) for ED mortality. Results were presented as aOR with 95% confidence intervals (CI) and determined significant at the level of $p<0.05$. Regression was adjusted for the following variables: age, sex, weekend admission, primary expected payer, median household income, hospital region and teaching status, previous AMI, thrombocytopenia, dyslipidaemia, smoking, anaemias, coagulopathy, diabetes mellitus, liver disease, malignancy, peripheral vascular disorders, chronic pulmonary disease and chronic renal failure. All statistical analyses were weighted and performed using SPSS version 27 (IBM Corp, Armonk, NY) [155].

This study did not require ethical approval. The NEDS is a publicly available national dataset and does not contain any patient-identifiable information.

Results:

A total of 8,577,028 selected ED encounters for CVD, including AMI, acute ischaemic stroke, AF, HF, PE, cardiac arrest and acute haemorrhagic stroke (**Supplementary Figure 1**) were recorded between 2016 and 2018. Overall, 5,120,843 (59.7%) had a low HFRS of <5, 3,041,699 (35.5%) had an intermediate HFRS of 5-15 and 414,485 (4.8%) had a high HFRS of >15 (**Table 1**).

Patients with a high HFRS had a higher prevalence of comorbidities such as dyslipidaemia (55.7%), thrombocytopaenia (6.1%), anaemia (25.0%), peripheral artery disease (3.5%) and chronic renal failure (34.7%), compared to patients with a low and intermediate HFRS ($p<0.001$ for all) (**Table 1**).

The most common cause of encounter was for AF (24.0%) followed by AMI (20.9%), ischaemic stroke (19.4%), HF (17.3%), PE (7.3%), cardiac arrest (5.8%) and haemorrhagic stroke (5.3%). The cohort admitted with ischaemic stroke had the highest proportion of patients with a high HFRS (16.7%), followed by haemorrhagic stroke, AMI and HF (10.6%, 1.7% and 1.7%). The cohort admitted with ischaemic stroke had the highest proportion of patients with an intermediate HFRS (57.5%), followed by haemorrhagic stroke (42.6%) and HF (40.5%). The cohort admitted with cardiac arrest had the highest proportion of patients with a low HFRS (89.1%), followed by AF (75.2%) and AMI (67.4%) **(Figure 1** and **Table 2)**.

Acute ischaemic stroke (66.9%) was the most common CVD encounter for the high HFRS group, followed by haemorrhagic stroke (11.7%) and AMI (7.2%). Ischaemic stroke was also the most common CVD encounter for the intermediate HFRS group (31.4%) followed by HF (19.8%) and AMI (18.3%). The most common cause of CVD encounter in the low HFRS group was AF (30.2%), followed by AMI (23.6%) and HF (16.8%) (**Figure 2**).

Patients admitted for AMI with a high HFRS were more likely to be older and female compared to those with an intermediate or low HFRS. These patients were more comorbid with conditions such as anaemia, thrombocytopaenia and peripheral vascular disorders compared to patients with a low HFRS ($p<0.001$). Similar findings were observed amongst the ischaemic stroke, HF, AF, and PE, cardiac arrest and haemorrhagic stroke cohorts (**Supplementary Table 2-9**). Patients with a high HFRS were more likely to be admitted as an inpatient (98.3% vs. 87.9% for intermediate HFRS and 47.2% for low HFRS), and less likely to be transferred to a short-term hospital (0.5% vs. 3.6% for intermediate HFRS and 13.0% for low HFRS), discharged to

home health care (0.2% vs. 0.6% for intermediate HFRS and 0.4% for low HFRS) and discharged home (0.5% vs. 5.7% for intermediate HFRS and 28.4% for low HFRS) (**Supplementary Table 9).**

Patients with a high HFRS generally had lower unadjusted rates of ED all-cause mortality compared to their lower frailty counterparts (0.1% vs. 0.8% for intermediate HFRS group and 7.9% for low HFRS group, p<0.001). However, high HFRS was associated with increased rates of overall mortality (ED and in-hospital combined mortality) (9.4% vs. 6.3% for intermediate HFRS group and 8.7% for low HFRS group, p<0.001). This trend was observed across all CVD admissions, with lower crude rates of ED all-cause mortality and increased rates of overall mortality with increasing HFRS category (**Table 2**).

On adjustment for baseline covariates, the high HFRS group had an decreased odds of ED mortality across all admission groups compared to their low frailty risk counterparts (p<0.001). However, the high HFRS group had increased odds of overall (ED and in-hospital) all-cause mortality across all admission groups compared to their low frailty risk counterparts (p<0.001). When looking at the effect size, patients with high HFRS admitted for AF had the highest odds of overall mortality (aOR 27.14 95% CI 25.03 to 29.43), compared to their low frailty risk counterparts (**Table 3 and Figure 3**).

With HFRS modelled as a continuous variable, increased HFRS was associated with significantly increased odds of hospitalisation and ED mortality across all selected CVD admissions per 1-unit increased of the HFRS (all p<0.001) (**Supplementary Table 10**).

Discussion

To the best of our knowledge, this is the first national analysis to examine the prevalence, clinical characteristics, cardiovascular phenotypes, and clinical outcomes of patients admitted to ED with a broad range of CVD conditions based on their frailty status. We report several important findings. Frailty is present in a significant proportion of CVD patients admitted to

the ED, with distinct cardiovascular phenotypes according to frailty status. Of the selected CVD diagnoses, ischaemic stroke was the most common encounter in the high HFRS group, followed by haemorrhagic stroke and AMI. Cardiac arrest was the most common encounter for the low HFRS group, followed by AF and AMI. Finally, higher frailty risk is associated with lower ED mortality, but increased admission to hospital and increased overall mortality across most CVD phenotypes [202-204].

Previous studies using frailty measures in general populations have estimated the prevalence of frailty to be between 1% to 91%, whereas studies in CVD cohorts have estimated it to be between 15% and 41% [16, 78]. This wide range in prevalence may relate to the heterogeneity between frailty measures and heterogenous populations [160]. There are few studies that utilise the HFRS and even fewer that use the HFRS in CVD cohorts, with most focusing on HF, acute coronary syndrome (ACS) and post-procedural outcomes from percutaneous coronary intervention or catheter ablation [89, 90, 95, 103]. One study used the HFRS in the ED cohort of 12,237 patients [159]. Interestingly, 17.5% of these patients had a high HFRS, 47.9% had an intermediate HFRS and 34.5% had a low HFRS. However, the study did not investigate CVD specific encounters but rather evaluated all encounters, and only included patients aged over 75 [159]. Elderly patients tend to be frailer, therefore the different distribution of HFRS observed in our study may reflect that the non-age-restricted ED population admitted for CVD is less frail.

We report variations in frailty status across the different CVD phenotypes. AF was a rare cause of admission in the high HFRS group but interestingly was associated with the worst overall prognosis when accounting for effect size. AF is associated with increasing age and comorbidity burden and increases stroke risk [58, 162, 163]. Frailty is also linked to the development of AF and it's sequalae through changes in left atrial volume in the ageing heart [162]. Frailty can be described as a relative contraindication to anticoagulation, depending on

the extent of the patient's frailty [165]. Therefore, highly frail patients are less likely to be anticoagulated, leading to the occurrence of thrombo-embolic complications [165]. Ischaemic stroke was the most common cause of encounter in the high and intermediate HFRS groups. Similar to AF, stroke is considered a condition of older age, with 70% of strokes occurring after the age of 65 [55]. There are no studies describing the prevalence of PE, cardiac arrest, and haemorrhagic stroke stratified by the presence of frailty in the ED setting.

Interestingly, cardiac arrest and had a high proportion of patients at low or intermediate risk of frailty. This could also be due to potential selection bias with only the most robust patients that are frail surviving to hospital admission. Cardiac arrest was associated with decreased odds of ED and overall mortality, which could be due to the inherent poor prognosis of the condition, independent of frailty status [68, 69, 72].

Intermediate and high frailty risk was also highly prevalent amongst HF encounters. Previous studies have investigated the prevalence of frailty using the HFRS and other risk scores [90, 102, 205, 206]. No studies have used the HFRS to study HF in the ED setting. In hospital studies, the reported prevalence of intermediate and high HFRS in HF are variable [90, 102]. A HF study of a US cohort estimated the prevalence of intermediate and high HFRS to be 19.9% and 0.1% respectively which agreed with an Australian study which reported a similar distribution and contrasts with another hospital study of Medicare beneficiaries who reported a prevalence of 47.4% and 25.0% for intermediate and high HFRS respectively [90, 91, 102]. This further demonstrates that this ED cohort may represent a clinically different group to those observed in hospital studies using the HFRS.

There are several important clinical implications of this study. Firstly, this study reaffirms frailty represents a significant proportion of patients seen in ED, with over 40% of patients at either intermediate or high risk of frailty. This outlines the importance of a frailty assessment in the ED [169-171]. Frailty and CVD are closely related; the increasing age of the population

and an improved survivorship of patients with acute and chronic CVD leads to the co-existence of CVD and frailty [6, 17]. CVD and frailty share a bidirectional relationship, with frailty associated with increased odds of CVD and vice-versa [16]. It is important to identify patients at risk of frailty, for appropriate management to prevent adverse complications and improve quality of life [172]. Moreover, frailty can be reversed, exemplifying the need for early identification and optimisation of risk factors [173]. Secondly, the coexistence of frailty and comorbidity among patients with CVD represents a challenge for healthcare services through increased length of stay, total costs, readmissions and mortality. Knowledge of the trends and outcomes of CVD in frail patients is important to deliver improved care for this at-risk group. Finally, this study prompts the early recognition and management of CVD and frailty in the community, which could have an impact on acute and unplanned encounters [174].

This study includes several limitations inherent to the NEDS database. Firstly, coded databases are susceptible to selection bias due to missing data, miscoding, and misdiagnosis. Secondly, given this is an observational study, confounding bias could not be eliminated despite the broad range of conditions covered by the NEDS. Thirdly, useful clinical information that could provide a more granular analysis such as race and pharmacological management of patients are not available in the NEDS. Most notably, previous studies have demonstrated that race and ethnicity are factors associated with inequality in access to care and increase risk of frailty [121, 207]. Fourthly, this analysis was based on US data, which cannot be generalised to other countries and health settings. Finally, detailed analysis of longitudinal outcomes could not be assessed as the NEDS only captures ED and in-hospital outcomes only.

In conclusion, ED encounters for CVD vary by frailty status with ischaemic stroke being the most common cause in high-risk patients, followed by haemorrhagic stroke and AMI, and cardiac arrest is the most common encounter in low-risk patients, followed by AF and AMI. Patient encounters for CVD in the ED have high frailty burden, which is associated with a

worse prognosis, including the highest overall mortality in patients with high HFRS, across most CVD phenotypes. Future studies are warranted to define the longitudinal association between frailty and mortality in this setting.

Appendix 12. STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) Checklist.

Section/Topic	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed

		Case-control study—If applicable, explain how matching of cases and controls was addressed. *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other Information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

Appendix 13. Paper published in the American Journal of Cardiology: Association of Frailty Status on the Causes and Outcomes of Patients Admitted with Cardiovascular Disease.

Introduction

Frailty is defined as an impairment of multiple systems resulting in an increased vulnerability to stress, leading to an increased risk of adverse outcomes such as hospitalisations and mortality, and is strongly associated with age [4]. With the growing numbers of the elderly population, the proportion of individuals living with frailty in society and across healthcare systems is increasing [3]. Similarly, the numbers of patients living with cardiovascular disease (CVD) is increasing, particularly given an improved survivorship in patients with acute or chronic CVD[157].

The relationship between frailty and CVD is bidirectional [20]. CVD is associated with a three-fold increase in frailty and frailty is independently associated with an increased mortality from CVD [21, 22]. A recent meta-analysis including 31,343 CVD patients reported that the prevalence of frailty was 17.9% and was associated with an increased risk of heart failure (HF)[16].

Previous studies have attempted to understand the underlying mechanisms linking older age and adverse CVD outcomes, with common mechanisms implicated being inflammation, concomitant risk factors and comorbidity burden [3]. However, there is little data investigating whether CVD admissions vary by frailty status and whether frailty is associated with in-hospital outcomes in patients admitted with acute CVD conditions. Knowledge on the specific causes of CVD admissions and their outcomes in relation to frailty status is fundamental in planning healthcare services around the growing needs of the population with frailty.

Therefore, the aim of this study was to describe the prevalence, clinical characteristics, and in-hospital mortality of patients with the CVD admissions of interest based on their frailty status, as measured by the Hospital Frailty Risk Score (HFRS).

Methods

The National Inpatient Sample (NIS) is the largest available database of US hospitalisations developed for the Healthcare Cost and Utilization Project (HCUP) sponsored by the Agency for Healthcare Research and Quality (AHRQ) [142]. The NIS contains anonymised data on diagnoses and procedures from over 7 million hospitalisations annually, representing a 20% stratified sample of all discharges from US community hospitals, excluding rehabilitation and long-term acute care hospitals [142].

The HFRS was developed by Gilbert et al. to establish whether elderly patients at risk of adverse outcomes could be identified using routinely collected healthcare data [10]. Briefly, a cohort of elderly (>74 years old) patients hospitalised with diagnoses associated with frailty were identified [10]. The HFRS was then created by grouping the identified patients according to their *International Classification of Diseases* 10^{th} revision (ICD-10) codes into 3 groups: low risk (HFRS <5), intermediate risk (HFRS 5-15) and high risk (HFRS >15) [10]. The score was then validated using a local and national UK cohort [10]. Each component of the HFRS and the associated weighting is outlined in **Appendix 1**.

Using ICD-10 codes (**Supplementary Table 1**), all adult discharge records with a principal diagnosis of an acute CVD admission between October 2015 and December 2019 were identified. This sample was further filtered by focusing on the 7 CVD admissions of interest: acute myocardial infarction (AMI), atrial fibrillation/flutter (AF), ischaemic stroke, HF, pulmonary embolism (PE), cardiac arrest and haemorrhagic stroke. The sample was further stratified according to their frailty status measured by the HFRS into 3 groups: low risk (HFRS <5), intermediate risk (HFRS 5 to 15) and high risk (HFRS >15) as defined by Gilbert et al [10]. Cases were excluded due to missing data for the following variables: age, sex, elective admission, in-hospital mortality, primary expected payer, total charges and length of stay. These cases accounted for no more than 1.0% of the original dataset. Cases not pertaining to one of the 7 diagnoses of interest were also excluded (**Supplementary Figure 1**). This

observational study was appraised according to the *Strengthening The Reporting of OBservational Studies in Epidemiology* (STROBE) recommendations (**Appendix 2**).

Continuous variables such as age, length of stay and total charges were summarised using median and interquartile range (IQR). Categorical variables were compared using the Chi-squared (X^2) test and summarised as percentages (%). Multivariable logistic regression was performed to determine the adjusted odds ratio (aOR) for all-cause mortality. Regression was adjusted for the following variables: age, sex, race, weekend admission, primary expected payer, median household income, bed size of hospital, region of hospital, location/teaching status of hospital, smoking status, previous myocardial infarction, previous percutaneous coronary intervention (PCI), previous coronary artery bypass graft (CABG), dyslipidaemia, and Elixhauser comorbidities (anaemias, coagulopathy, diabetes mellitus, liver disease, metastatic cancer, peripheral vascular disease and chronic renal failure). Results were presented as adjusted odds ratios (aOR) with 95% confidence intervals (CI). Results were determined significant at the level of $p<0.05$. All statistical analyses were weighted and performed using SPSS version 27 (IBM Corp, Armonk, NY) [155].

Results

A total of 9,317,398 discharges had one of the 7 CVD diagnoses of interest (AMI, ischaemic stroke, AF, HF, PE, and haemorrhagic stroke) (**Supplementary Figure 1**). Overall, 5,573,033 discharges (59.8%) had a HFRS of <5, 3,422,700 (36.7%) had a HFRS of 5-15 and 321,665 (3.5%) had a HFRS of >15 (**Table 1**).

Patients with a HFRS >15 were more likely to be older (median age 75 vs. 73 for HFRS 5-15 group and 68 for HFRS <5 group) and female (54.1% vs. 48.7% for HFRS 5-15 group and 43.0% for HFRS <5 group) and have a higher prevalence of hypertension, coagulopathy and thrombocytopaenia, as well as a lower prevalence of previous AMI, previous PCI, previous

CABG, HF and diabetes, compared to patients with a HFRS <5 and HFRS 5-15 (p<0.001 for all) (**Table 1**).

The most common cause of admission was AMI (28.7%) followed by ischaemic stroke (23.8%), AF (21.0%), HF (16.2%), haemorrhagic stroke (5.9%), PE (4.0%) and cardiac arrest (0.4%). The cohort admitted with ischaemic stroke had the highest proportion of patients with a HFRS >15 (10.8%), followed by haemorrhagic stroke and cardiac arrest (9.1% and 2.5%). Similarly, cohorts admitted with cardiac arrest had the highest proportion of patients with a HFRS 5-15 (70.4%), followed by ischaemic stroke and haemorrhagic stroke (66.9% and 54.9%). The cohort admitted with AF had the highest proportion of patients with a HFRS <5, followed by AMI and PE (80.3% vs. 76.7% and 74.1%) **(Figure 1)**.

The most common cause of CVD admission in the HFRS <5 cohort was AMI (36.9%), followed by AF (28.2%) and HF (17.4%). Ischaemic stroke was the most common CVD admission for the HFRS 5-15 (43.3%) followed by AMI (17.8%) and HF (15.6%). Similarly, ischaemic stroke was the most common CVD admission for the HFRS of >15 (75.4%) groups and followed by haemorrhagic stroke (15.5%) and AMI (4.3%) (**Figure 2**).

Patients with HFRS >15 had higher unadjusted rates of all-cause mortality compared to their lower frailty counterparts (10.3% vs. 7.6 for HFRS 5-15 group and 2.2% for HFRS <5 group, p<0.001). Increased unadjusted rates of all-cause mortality for high risk frailty patients was also observed in patients admitted with AMI, ischaemic stroke, AF, HF and PE, but not for patients admitted with cardiac arrest or haemorrhagic stroke (all p<0.001) (**Table 2** and **Supplementary Figure 2**).

On adjustment for baseline covariates, increasing frailty risk was associated increased odds of all-cause mortality. Patients with a HFRS of 5-15 or HFRS >15 admitted for AF had the highest odds of all-cause mortality (aOR 17.69, 95% CI 16.08 to 19.45 for HFRS >15 group, aOR 6.75, 95% CI 6.51 to 7.00 for HFRS 5-15 group). Increased odds of mortality were observed with

worsening frailty status across a broad range of different CVD causes for admission. For HFRS >15 group was associated with in an increased odds of mortality for patients admitted with AMI, ischaemic stroke, HF, and PE admission diagnoses ($p<0.001$). Interestingly, a decreased odds of mortality in the HFRS >15 group was observed in patients admitted for cardiac arrest and haemorrhagic stroke only (aOR 0.46, 95% CI 0.39 to 0.55 for cardiac arrest patients with a HFRS >15, aOR 0.86, 95% CI 0.83 to 0.88 for haemorrhagic stroke patients with a HFRS >15) (**Table 3 and Figure 3**).

Discussion

This is the first study to examine the prevalence, clinical characteristics and in-hospital mortality of patients admitted with a broad range of acute CV presentations on a nationwide scale based on their frailty status. We report several important findings. Firstly, we report the most common CVD admissions across frailty categories, with AMI being the most common in patients with a low frailty score, and ischaemic stroke being the most common in patients with an intermediate and high frailty score. Secondly, we report important frailty-based differences in baseline characteristics across patients with different CVD admission diagnoses. Finally, patients with an intermediate and high frailty score had increased all-cause mortality compared with their counterparts with lower risk across most CVD admission diagnoses, except in cardiac arrest and haemorrhagic stroke categories.

The association between frailty and CVD has been widely explored in the literature [3, 16, 20-22]. Frailty has been shown to be a predictor of incident CVD [22, 158]. CVD is associated with a three-fold increase in prevalent frailty, and frailty increases odds of CVD by 35% [22]. This relationship is believed to be due to similar underlying biological pathways [22]. Both CVD and frailty share similar biomarkers such as interleukin 6, high levels of factor VIII, d-dimer, fibrinogen, and C-reactive protein [208-210]. The pathways in conjunction with low physical activity and poor nutrition, could lead to decreased physiological reserves and

increased susceptibility to stress, leading to frailty [177]. In addition, these factors can lead to a pro-thrombotic state, and increased levels of inflammation, leading to increased risk of cardiovascular events and adverse outcomes [208-210].

The HFRS was nationally validated using a cohort of over 1 million UK patients, of which 37.6% had an intermediate risk of frailty and 20% had a high risk of frailty [10]. In our cohort of 9 million US patients hospitalised with CVD, there was a lower proportion of patients at intermediate or high risk of frailty. The prevalence of frailty amongst overall CVD patients was previously estimated between 15% and 19% [9, 16, 177], as well as up to 40.9% in studies utilising HFRS [101, 102]. Variable prevalence of frailty in the literature could be partially explained by differences in the cohorts studied, but also importantly differences in definitions utilised and what is considered to represent frailty, with studies using definitions derived from Rockwood et al., Fried et al. and Gill et al [9-11, 16, 211]. There is a challenge to defining frailty as there is no standardised measurement, but HFRS represents a potentially advantageous option due to its dependence on the widely available ICD coding system [178]. The HFRS follows the deficit model (combining impairments) and has been validated against the Rockwood and Fried scores, however it can be quite challenging for clinicians to calculate due to lack of automated computation [90]. Similar to other studies, we observed that patients with increasing frailty are likely to be older, female, have longer hospital stays and total costs [3, 10, 16, 21, 90, 102].

This study found important variations in frailty status across different CVD admissions. Amongst patients with intermediate or high frailty risk, the most prevalent CVD admission was acute ischaemic stroke. This is may be explained by the inclusion of the sequelae of stroke in the HFRS, but other contributors such as older age, which increases the risk of both stroke and frailty, with 70% of strokes occurring after the age of 65, are also important [55]. AF has been reported to be prevalent in 15% of the frail population, although we report an interesting pattern

of decreasing proportion of AF admission with increasing frailty [164]. Again, this could be mediated by varying definitions of frailty as the previous study used scores devised by Fried et al. and Rockwood et al. [164]. Studies using the HFRS demonstrated a similar distribution of frailty status to this study among patients with AF, with most patients at low risk of frailty, and only a small percentage at high risk of frailty [179]. This study shows admission for HF decreases with increasing frailty yet is still common with over 3 in 10 patients admitted with HF at intermediate or high risk of frailty. Our findings are supported by other studies that show intermediate or high risk of frailty is present in up to 1 in 5 hospitalised HF patients and is associated with a longer length of stay and increased total charges [90, 103]. This could be explained by an increased number of comorbidities in the HF population, with a high prevalence of dyslipidaemia, anaemia and hypertension [90]. This agrees with multiple studies that demonstrate patients with increased HFRS have higher Charlson comorbidity score, in line with the HFRS being based on the total comorbidity burden of patients [10, 90, 102]. There are no studies describing the prevalence of PE, cardiac arrest, and haemorrhagic stroke among hospitalised frail patients.

Interestingly, AF was a rare cause of admission in the high-risk group but was associated with the worst prognosis in these patients. The association between AF and mortality has been reported in multiple studies, as the prevalence of AF increases with age, comorbidity burden, and increases the risk of stroke and its associated complications [162, 163]. Studies have suggested that patients with frailty also have a larger left atrial volume, which is one of the main cardiac abnormalities linked to the development of AF and systolic dysfunction [180]. Furthermore, patients with incident AF are commonly anticoagulated, which increases risk of bleeding and further complications such as haemorrhage [162]. However, studies report that AF patients with increasing frailty are less likely to be treated with oral anticoagulants, which can lead to increased likelihood of downstream thrombotic events and poorer outcomes [179,

180]. We report that HF was independently associated with higher odds of mortality with increasing frailty, as seen in other studies [90, 103]. Our findings of cardiac arrest and haemorrhagic stroke, whilst different to the other CVD admissions of interest, could have several explanations. These conditions have substantial mortality *per se* with little modification by HFRS. This analysis encompassed only patients that were admitted due to cardiac arrest leading to potential selection bias, and so it is possible that many of the frail patients did not survive to admission and only ones with the most favourable prognosis survived to admission. It is possible that the poor outcomes in these patient groups occur independent of frailty status [69, 183].

There are important clinical implications of this study. This study demonstrates that patients with intermediate to high frailty risk represent a substantial portion of population admitted for CVD and raises the importance of frailty assessment by cardiologists. A co-existence of frailty and CVD is becoming even more important due to an aging population with higher morbidity burden. Frail patients admitted with CVD have higher mortality rates and burden the healthcare system, and knowledge of the trends in CVD admission is fundamental to improve the outcomes of this clinically at-risk population. This study may support the early identification and management of CVD in frail patients, particular in primary care, although whether this would impact on acute admissions is unknown.

This study has several limitations inherent to the use of the NIS database. Firstly, coded data for the NIS could be subject to selection bias due to inaccurate coding or missing data. Secondly, detailed clinical information such as pharmacological treatment that can mediate outcomes could not be investigated due to their lack of availability with the NIS. The impact of differential pharmacological management in the frail population on outcomes may be an area for further research. Thirdly, as this is an observational study, confounding bias could not be fully eliminated despite the broad scope of conditions covered by the NIS, and therefore

causality between frailty, CVD admission and mortality cannot be proven. Finally, the NIS only captures information on in-hospital events and therefore, more detailed analysis of longitudinal outcomes could not be assessed [184].

In conclusion, the causes of CVD admission vary with frailty status with AMI being the most common in patients with a low risk of frailty, whereas ischaemic stroke being most common in patients with intermediate or high risk of frailty. Increasing frailty in patients admitted for AMI, ischaemic stroke, AF, HF and PE is associated with an increased all-cause mortality. Future, more granular studies are necessary to guide care and improve the CVD outcomes in frail patients in an ever-aging population.