Assessing the impact of comorbidity measures on outcomes following acute coronary syndrome

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Abstract

Acute coronary syndromes (ACS) are a common acute presentation of cardiovascular disease (CVD) associated with significant morbidity, mortality and societal economic burden. With improvements in medical care and post-ACS survival rates, ACS patients are increasingly living with multiple comorbidities. It is recommended that comorbidity burden be considered in clinical decision-making but there are critical gaps in current knowledge, particularly on the relative merits of available measures of comorbidity. This thesis was designed to address some of these through a series of linked studies.

In Part 1 a systematic review of published literature identified five comorbidity measures used to predict the outcomes of ACS patients. The Charlson Comorbidity Index (CCI) appeared the most widely validated and commonly used, but most comorbidity measures demonstrated an association between worse prognosis and greater comorbidity. In Part 2, analyses of large-scale US National Inpatient Sample (NIS) data from 2004-2014 quantified the trend over time towards greater comorbidity among admitted ACS patients defined using the CCI and the Elixhauser Comorbidity Score (ECS). These analyses also provided estimates of the poorer outcomes, lower levels of invasive treatment, and longer stay and higher costs among those with higher comorbidity burden. In Part 3, a direct head-to-head comparison of the prognostic performance of CCI and ECS is reported, in which the ECS was found to have superior discrimination and goodness-of-fit in predicting important in-hospital adverse outcomes. The CCI and ECS differ in the comorbidities they include, the weights assigned to them, and the accepted cut-points for categorisation. In Part 4, an agreement analysis found relatively low agreement between the two measures when classifying level of comorbidity in ACS patients.

This nationwide analysis of more than 7 million ACS hospitalisations emphasizes the importance of objective comorbidity burden assessment to guide to management strategy and reliably assess prognosis at ACS patients. Clinical implications and further areas of research are discussed in detail.

Publications

Publications arising directly from this PhD thesis are as follow:

Published papers:

1. Zhang, F., Bharadwaj, A., Mohamed, M. O., Ensor, J., Peat, G., & Mamas, M. A. (2020). Impact of Charlson co-morbidity index score on management and outcomes after acute coronary syndrome. The American Journal of Cardiology, 130, 15-23.
2. Zhang, F., Mohamed, M. O., Ensor, J., Peat, G., & Mamas, M. A. (2020). Temporal trends in comorbidity burden and impact on prognosis in patients with acute coronary syndrome using the Elixhauser comorbidity index score. The American journal of cardiology, 125(11), 1603-1611.
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4. Zhang, F., Chiu, Y., Ensor, J., Mohamed, M. O., Peat, G., & Mamas, M. A. (2022). Elixhauser outperformed Charlson comorbidity index in prognostic value after ACS: insights from a national registry. Journal of Clinical Epidemiology, 141, 26-35.

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List of Abbreviations

Acute Coronary Syndrome	ACS
Acute Myocardial Infarction	AMI
Akaike Information Criterion	AIC
American Hospital Association	AHA
Bayesian Information Criterion	BIC
British Heart Foundation	BHF
Cardiovascular	CV
Cardiovascular Disease	CVD
Charlson Comorbidity Index	CCI
Chronic Comorbidity score	CS
Chronic Pulmonary Disease	CPOD
Clinical Classification of Software	CCS
Confidence Interval	CI
Coronary Angiography	CA
Coronary Artery Bypass Grafting	CABG
Coronary Heart Disease	CHD
Diabetes Uncomplicated	DM
Electrocardiography	ECG
Elixhauser Comorbidity Score	ECS
European Society of Cardiology	ESC
Fluid-electrolyte Disorders	LYTES
Global Registry of Acute Coronary Events	GRACE
Hazard Ratio	HR
Healthcare Cost and Utilization Project	HCUP

Healthcare Research and Quality	AHRQ
Heat Failure	HF
International Classification of Diseases, Ninth Revision, Clinical Modification	ICD-9-CM
International Classification of Diseases, Tenth Revision, Clinical Modification/Procedure Coding System	ICD-10-CM/PCS
Interquartile Range	IQR
Intra-aortic Balloon Pump	IABP
Major Acute Cardiovascular & Cerebrovascular Events	MACCE
Major Acute Cardiovascular Events	MACE
Multiple Imputations by Chained Equations	MICE
National (Nationwide) Inpatient Sample	NIS
National Institute for Health and Care Excellence	NICE
Non-ST-elevation Acute Coronary Syndrome	NSTEACS
Non-ST-elevation Acute Myocardial Infarction	NSTEMI
Not Available	NA
Number of Elixhauser Comorbidities	NEC
Odds Ratio	OR
Percutaneous Coronary Intervention	PCI
Peripheral Vascular Disease	PCV
Quality In Prognostic factor Studies	QUIPS
Relative Risk	RR
Reporting of studies Conducted using Observational Routinely collected Data	RECORD
Risk of Bias	RoB

Simple Comorbidity Index	SCI
Simplified Comorbidity Measure	SCM
Soroka Acute Myocardial Infarction	SAMI
Stand Deviation	SD
ST-elevation Acute Myocardial Infarction	STEMI
Strengthening The Reporting of Observational Studies in Epidemiology	STROBE
Thrombolysis in Myocardial Infarction risk score	TIMI risk score
United States	US

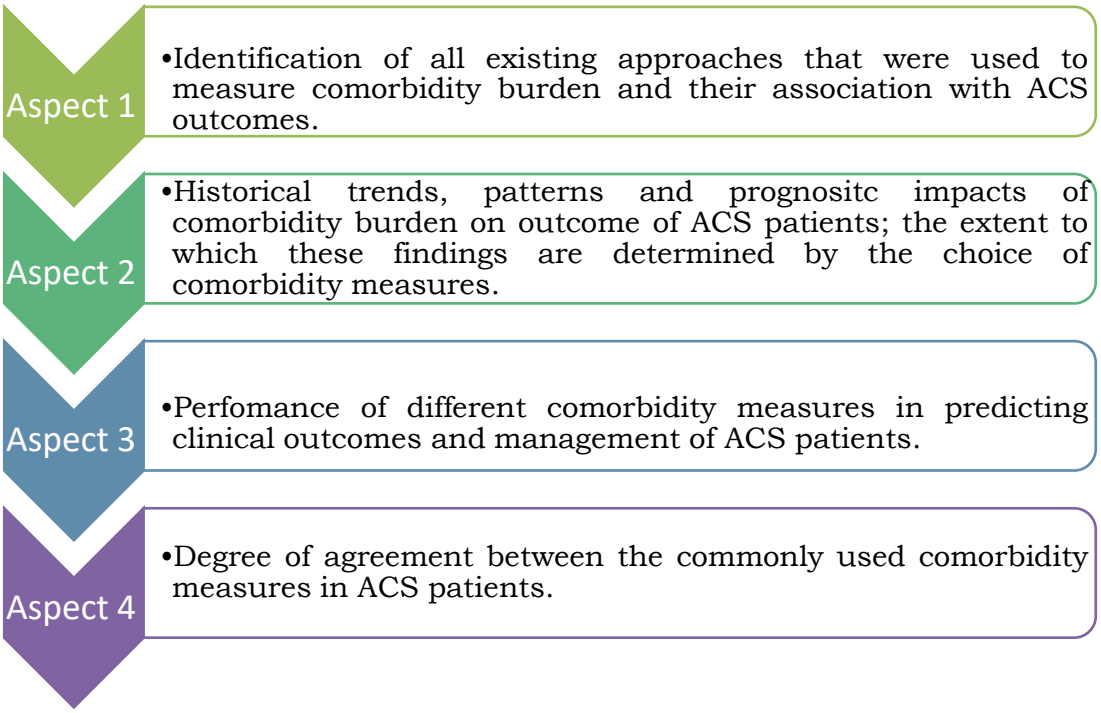
Chapter 1 - Overview of Thesis

This chapter includes the introduction of this thesis and provides a brief outline for each chapter.

1.1 INTRODUCTION

This thesis is concerned with the circumstances of comorbidity burden in patients with acute coronary syndromes (ACS). It considers the comorbidity burden in ACS patients in a multifaceted manner, by moving in complexity from using different established comorbidity scores on the exploration of ACS prognosis, to comparing the prognostic performance of different comorbidity measures to finally investigating the degree of agreement between different comorbidity measures. On the whole, this thesis can be divided into four parts, in order to study the four aspects of comorbidity measures and ACS prognosis as illustrated in **Figure 1.1**.

Figure 1.1: Pictorial demonstration of the four main aspects of the thesis.



1.2 OBJECTIVES

Hence, in order to achieve the aforementioned four aspects, the thesis, addressed through a systematic review of published literature and a series of studies analysing a nationwide database of hospitalisation of ACS patients, was

designed into four main objectives:

1) To identify existing comorbidity measures that have been used in patients admitted with a diagnosis of ACS and summarise their associations with ACS outcomes.
2) To explore the temporal trends in baseline characteristics, risk profile, comorbidity burden, use of treatments and clinical outcomes of ACS patients over years, how these factors change among different groups stratified by different comorbidity measures, and how patients' comorbidity burden are associated with ACS outcomes and the use of an invasive strategy, based on different comorbidity measures.
3) To compare which comorbidity measure has better prognostic value in predicting ACS managements and outcomes.
4) To investigate if there is any difference between commonly used comorbidity measures on classifying patients into same-level comorbid burden groups.

1.3 ORGANISATION AND CONTENT OF THESIS

1.3.1 Chapter 2

This chapter is divided into two domains, in order to provide an overview of the background of this thesis. Firstly, it describes the pathophysiology, clinical manifestations and diagnosis of different types of ACS. In addition, risk factors, overall management (including invasive strategies) and outcomes of ACS patients and the prevalence of ACS are discussed. Second, an overview of definitions of comorbidity and comorbidity measures is introduced in detail, with types of comorbidity measures and their impacts on ACS patients also included.

1.3.2 Chapter 3

This chapter mainly addresses Objective One of this thesis. It conducts a systematic review that identified existing comorbidity measures used to study the impact of comorbid burden on ACS patients and summarised the results of these studies. Meanwhile, it highlights the gaps in evidence for this thesis.

1.3.3 Chapter 4

This chapter describes the database used for the subsequent objectives, which is the National Inpatient Sample (NIS). Furthermore, the whole process of making the dataset ready to use for the preliminary analyses in each chapter is described. Further data processing strategies according to each goal can be found in the following chapters.

1.3.4 Chapter 5

This chapter mainly addresses Objective Two of the thesis. In this chapter, the temporal trend in characteristics, risk factors, receipt of treatments, comorbidities of ACS patients were studied, their changes across comorbid burden groups stratified by the Charlson Comorbidity Index (CCI) measure were also explored. Finally, the impact of comorbid burden defined by the CCI on clinical outcomes and the use of invasive treatments in ACS patients was studied.

1.3.5 Chapter 6

In line with Objective Two of the thesis, this chapter studies how patient demographics, comorbidities, treatments and clinical outcomes changed over different groups classified by different ways using the Elixhauser Comorbidity Score (ECS) method. In addition, I explored the associations between comorbid

burden defined by the ECS method and in-hospital invasive strategy and clinical outcomes in a national cohort of patients admitted with ACS.

1.3.6 Chapter 7

Objective Three of the thesis was addressed in this chapter. Drawbacks in previous comparison studies using the ECS and CCI limited their reliability in contemporary practice, this chapter compares the prognostic value of the CCI and ECS in predicting clinical outcomes using their scoring systems in ACS patients using data from a nationwide administrative database.

1.3.7 Chapter 8

This chapter is related to Objective Four of the thesis. There has been no study researching whether the two common comorbidity measures identify different groups of patients within a population, this chapter investigates overlap between the CCI and ECS in a national cohort of patients with ACS, and describe differences in patient characteristics, comorbidities, receipt of treatments and clinical outcomes stratified by different ECS/CCI combinations.

1.3.8 Chapter 9

This chapter mainly discusses the overall findings, strengths, limitations of this thesis and the potential implications of these findings on future research or clinical practice.

Chapter 2 - Background

This chapter provides an introduction to ACS, comorbidity, comorbidity measure, and background for this thesis.

2.1 ACUTE CORONARY SYNDROME (ACS)

2.1.1 Pathophysiology

This thesis mainly concerns the population with the acute coronary syndrome (ACS). ACS is the medical name for a heart attack, which occurs in the presence of acute myocardial injury due to an acute thrombotic occlusion in the coronary arteries resulting in the decrease of blood and oxygen to the heart muscle [1-3].

Pathologically, the majority of ACS is caused by coronary heart disease (CHD) and the root reason for CHD is a process of atherosclerosis, which usually begins within the first ten years of life [4, 5]. During this period, cholesterol and fatty substances called plaques or atheroma accumulate within the walls of arteries causing the arteries to harden and narrow. The mechanisms underlying the development of atherosclerosis are complicated, and there are many theories [5, 6]. The most broadly accepted one is the "the response to endothelial injury" theory: the main risk factors of ACS eventually damage the arterial intima, while the formation of the atherosclerotic lesion is the result of an inflammatory-fibroproliferative response of arteries to endothelial and intimal injury. During this inflammation-fibrosis process, cholesterol-rich plaques or atherosclerotic plaques are deposited in the blood vessel wall, and the expansion and proliferation of muscle cells in the blood vessel wall form a hard covering on the plaque, leading to swelling or fibroatheroma, which grows into the middle of blood vessels.

Usually, atherosclerosis develops slowly and there are no symptoms related to its existence. However, when a rupture or fissure of a vulnerable atherosclerotic plaque in a coronary artery occurs, which causes activation of platelet and clotting factors. This rupture and activation of clotting factors can

promote the formation of a clot resulting in a blockage of the coronary artery. This reduces or even stops blood flow to the heart resulting in damage or death of the heart muscle, which is ACS [3].

All types of ACS are mainly divided into two groups, ST-elevation acute myocardial infarction (STEMI) and Non-ST-elevation acute myocardial infarction (NSTEMI) [1]. STEMI occurs when there is complete blockage of one or more heart arteries and can be diagnosed by performing an electrocardiogram which will show typical features of having this type of ACS [7]. On the other hand, NSTEMI usually occurs due to a sudden reduction in blood supply to the heart muscle from rupture of a plaque without complete occlusion of the coronary artery or a supply demand mismatch [8]. STEMI and NSTEMI are both types of acute myocardial infarction (AMI). Unstable angina (UA) is also considered to be a kind of ACS, although there is no myonecrosis in this condition, and occurs when angina episodes are experienced at low workload/at rest [9]. All three clinical syndromes are collectively referred to as ACS.

2.1.2 Symptoms

Clinical presentation of ACS varies from one person to another. However, the common symptoms of ACS [10] are chest pain or discomfort often radiating to other areas such as the shoulders, arms, neck, back, jaw or stomach. Other symptoms may include cold sweat, feeling light-headed, nausea, feeling tired or shortness of breath. However, these symptoms are “atypical”, with pain experienced in different ways or even absent. Approximately 30% of people may not have the typical symptoms as outlined above, especially the elderly, women, or those with diabetes which may predispose to nerve damage which can affect the feeling of pain.

2.1.3 Diagnoses

The initial diagnosis of a patient with a suspected ACS generally includes assessment of symptoms, clinical history, electrocardiography (ECG) and cardiac biomarkers [10]. Although chest discomfort is a typical symptom of ACS, the description of such chest pain has little utility in aiding diagnosis as it is not specific for ACS. Hence, a complete diagnosis requires other methods. Clinical history can assist in the diagnosis of ACS and provide comparative data for blood tests and ECG in the future. ECG plays an important role in the diagnosis of ACS and should be performed as early as practicable. The ECG patterns are important for distinguishing between NSTEMI and STEMI. Blood testing is undertaken to detect evidence of myonecrosis through the detection of substances released by damaged myocardium into the bloodstream. There are many different biomarkers used to determine the presence of myocardial damage [11]. The most commonly used biomarker in clinical practice is troponin, owing to its higher sensitivity and specificity for measuring myocardial damage than other biomarkers. Troponin levels begin to rise within 2-3 hours of myocardial injury and peak at 18-24 hours [12].

2.1.4 Risk Factors

Risk factors for developing an ACS are divided into two general categories: non-modifiable and modifiable. Non-modifiable risk factors include age, gender and family history. The risk increases with age and is greater in men and in people with a family history [13].

Modifiable risk factors include smoking, alcohol intake, hypertension, diabetes, dyslipidemia, obesity, psychosocial factors, lack of exercise, poor diet, metabolic disorders and other less established risk factors [14]. People with the above risk factors are more likely to develop an ACS and these factors also affect

the prognosis of ACS. Noticeably, although alcohol intake is generally regarded as a risk factor for cardiovascular diseases, there have been counter-intuitive findings in recent studies related to ACS [15, 16]. A population-based cohort study [15] showed that non-drinkers had the highest increased risk for AMI compared to moderate drinkers; former drinkers and occasional drinkers followed, both also had increased risk while the increased risk in occasional drinkers was attenuated; meanwhile, heavy drinkers were even at a lower risk of AMI compared to moderate drinkers. This study also showed that non-drinkers still had a higher risk for UA compared to moderate drinkers, however, former drinkers, occasional drinkers, and heavy drinkers were no significant difference in risk for UA with moderate drinkers. In addition, many studies have demonstrated that light-to-moderate alcohol consumption may be cardio-protective among apparently healthy individuals [15-17]. However, no firm evidence of its protective effect was present for ACS patients [15].

In addition, the other factors that may have an impact on the prognosis of ACS also include race, income and the medication history or surgical history after hospitalisation with ACS, such as long-term use of anticoagulants, prior percutaneous coronary intervention (PCI), and prior coronary artery bypass grafting (CABG).

2.1.5 Management

ACS is a life-threatening condition and patients must receive immediate medical attention. The overall goal is generally aimed to restore coronary blood flow, enable the delivery of oxygen and nutrients to the heart, and minimise irreversible myocardial injury as well as the risk of future ACS. The treatment of ACS generally depends on the type of clinical syndrome, STEMI or NSTEMI. Given the treatments on them are different, It will be discussed separately

according to the two types of ACS [12, 18].

STEMI

Invasive strategy

Since STEMI occurs when the artery is completely occluded and the diagnosis can be confirmed on ECG, treatment should be based on the principle of "time is muscle". If the patients presenting with chest pain and diagnosed with STEMI, it requires emergency reperfusion treatment to open the blocked parts and restore coronary flow within the recommended timeframe of 90 minutes after the onset of symptoms. PCI is the preferred reperfusion strategy for STEMI treatment [19]. PCI involves insertion of a thin catheter through an artery either in the leg or the wrist, that is guided to the coronary arteries under x-ray guidance. Interventional cardiologists use this catheter to inject contrast dye into the coronary arteries to determine if there is any stenosis/blockage in the arteries [20]. A wire is passed through the narrowing or occlusion in the coronary artery and is used to deliver balloon that can be inflated within the artery to disrupt the blood clot and compress the atheroma against the wall of the blood vessel, which can re-establish blood flow within the artery. In order to prevent the recurrence of narrowing in the vessel, metal tubes called stents are placed after the original ballooning. The NICE (National Institute for Health and Care Excellence) quality standards call for PCI to be performed as soon as possible after hospital arrival, it is ideal if it can be performed in a timely manner within 90 minutes [21]. Any delay is associated with higher mortality [22]. After PCI, patients are usually indefinitely treated with aspirin and dual antiplatelet therapy (usually aspirin and clopidogrel) for at least 12 months [23, 24].

However, when the PCI facilities are not available immediately or are administered outside the recommended timeframe of 90 minutes, thrombolytic therapy should be located with drugs such as alteplase or reteplase [25]. These

drugs can break down fibrin (the substance which forms the mesh of a clot) by activating the tissue plasminogen to allow immediate desolation of thrombus inside the coronary arteries. Then, these patients can be transferred to a PCI capable hospital for invasive coronary angiography followed by PCI or CABG if necessary. Unfortunately, thrombolytic drugs can increase the risk of bleeding complications [26], which is dangerous in patients who had a previous stroke, have high blood pressure or had recent surgery. Hence, these drugs must be used carefully in such patients.

Pharmacological treatments

In order to inhibit the activation and aggregation of platelets, aspirin loading should be accompanied by a loading dose of a P2Y12 receptor antagonist. Current guidelines recommend the administration of aspirin along with one of the P2Y12 receptor antagonist such as clopidogrel, prasugrel or ticagrelor for up to 12 months depending on the indication and patient risk factor profile. In addition, heparin is also used in the treatment of ACS by inhibiting the coagulation pathway and the formation of blood clots [27, 28].

NSTEMI

NSTEMI patients do not usually require immediate intervention in the form of PCI, although depending on the risk profile, may require PCI within the first 24 hrs of admission for high-risk cases [29]. However, similar to STEMI treatment, national bodies emphasise patients with NSTEMI should also receive appropriate medications such as antiplatelets (aspirin, clopidogrel, etc.) and antithrombotics (heparin, glycoprotein 2b3a) [13]. Then, the decision about an invasive strategy in form of coronary angiography or PCI is made by the estimated six-month mortality risk using the Global Registry of Acute Coronary Events (GRACE) risk score as a guide [30]. The NICE quality standard requires cardiac catheterization in patients with a 6-month mortality rate of 3.0% or

higher as calculated using GRACE score, within the first 72 hours after admission, with an assessment of whether coronary artery revascularization is required [31].

In the context of NSTEMI, an invasive strategy is defined as the use of a procedure called "coronary angiography (CA)" to conduct an initial assessment of coronary anatomy [20], if significant coronary artery disease is identified, revascularisation in the form of PCI or CABG is needed. CA is the most frequently performed procedure, in which a catheter is inserted into the coronary artery through the femoral artery or radial artery so that the operator can visualize the degree of coronary artery blockage by injecting contrast dye into the coronary artery under X-ray guidance and identify the culprit lesion in the vessel that causes NSTEMI. The information from CA can also help determine the further options of treatment in form of medical management, PCI or CABG. In total, depending on the patient's risk profile, management could involve a combination of antiplatelet/anticoagulant therapy, or a combination of angiography/PCI, or a combination of both. UA has similar pathophysiology to NSTEMI [12]. Hence, for NSTEMI/UA, the clinical management strategy is similar. In this thesis, main invasive strategies include the use of either CA or PCI.

2.1.6 Outcomes

One of the most serious outcomes of ACS is death. ACS is one of the most common causes of death around the world with more than 4 million deaths estimated to be caused by ACS in Europe [12]. At the same time, numerous complications can occur as a result of ACS, which can vary widely from mild to life-threatening. I list some of them in the following:

Arrhythmia and conduction disturbances

Under Physiological conditions, the heart beats at a regular sinus rhythm. When a heart beats too fast or too slowly at an irregular rate, this condition is called arrhythmia.

Re-infarction

Re-infarction is a serious complication that can occur in patients after ACS and is a major cause of morbidity and mortality after primary PCI. Even in the contemporary PCI era, re-infarction still occurs in 1 in 14 patients within 3 years. It is a heterogeneous entity with a complex pathophysiology and can extend the damage caused by ACS, leading to hospitalisation and worsening the course of ACS [32].

Mechanical dysfunction and Inflammatory complications

Patients are at risk of multiple cardiac complications after ACS, some of them are mechanical complications and subsequent inflammatory complications, they are related to the location and degree of myocardial injury. For example: pericardial effusion, cardiac tamponade, coronary dissection [33].

Pericardial effusion is often secondary to heart muscle rupture or injury after ACS. The normal pericardium is surrounded by a fibrous sac that consists of two thin layers. Normally, there is a small amount of fluid between them. However, pericardial effusion occurs when extra fluid builds up between these two layers. In some cases, pericardial effusion can develop rapidly, too much fluid builds up and then develops into cardiac tamponade.

Cardiac tamponade can happen when a coronary artery rupture or perforation leads to blood flowing out of the vessel to the pericardium. When extra fluid or blood builds up in the space between the pericardium and the heart, resulting in cardiac tamponade. This extra fluid compresses the heart and restricts it from pumping enough blood to the rest of the body. This is rapidly fatal unless treated promptly [34].

Coronary artery dissection refers to the separation of the intimal lining from the outer vessel wall caused by either an intimal tearing from the vasa vasorum or hemorrhage, resulting in the formation of a true lumen and a thrombus containing a false lumen. It can affect or block the blood flow of the coronary arteries and can cause myonecrosis which can be fatal.

Pericardiocentesis is the most useful procedure for the early treatment or diagnosis of pericardial effusion and cardiac tamponade. It is conducted using a needle and a small catheter through the chest wall and into the tissue around the heart to drain the fluid in the sac around the heart.

Vascular injury

The implantation of a stent requires multiple operations in the coronary arteries with the help of many devices. For example, the guidewire and balloon pass through the stenosis lesion, and the balloon and stent expand the blood vessel at the stenosis. These mechanical operations may cause damage to the blood vessels due to the fragile and narrowed coronary arteries.

Stroke

A stroke happens when the oxygen or blood supply to the brain is blocked or cut off by a clot or a ruptured plaque. Stroke remains a catastrophic complication of ACS, with an increase of 30% in-hospital and long-term mortality within patients with stroke following an ACS compared with a matched cohort of stroke patients without a preceding ACS [35].

Major Bleeding

Major bleeding includes any gastrointestinal, intracranial, retroperitoneal and procedure-related haemorrhages. Almost half of the patients with ACS have a higher risk of bleeding, which is associated with a roughly 5-fold increase in mortality [36]. The relationship between iatrogenic bleeding and higher mortality is increasingly recognized. Increasingly the use of multiple

antithrombotic drugs and invasive strategies has increased the risk of bleeding in AMI [37, 38].

In this thesis, ACS outcomes include mortality, MACCE (Major Acute Cardiovascular & Cerebrovascular Events) and major bleeding. MACCE is defined as a composite of mortality, cardiac complications, acute ischemic stroke, and vascular injury. Cardiac complications include any event of pericardial effusion, cardiac tamponade, coronary dissection or need for pericardiocentesis. Major bleeding includes any gastrointestinal, intracranial, retroperitoneal and procedure-related hemorrhages.

2.1.7 Epidemiology

Cardiovascular disease (CVD) remains the leading cause of death globally, with an estimated 17.9 million deaths in 2019, representing 32% of all global deaths. ACS is a common manifestation of CVD and is associated with significant morbidity, mortality and economic burden to society [39].

Of all global deaths from CVDs, 85% of deaths are due to ACS and stroke [40]. According to the British Heart Foundation (BHF) statistical reports in 2021, approximately more than 100,000 hospital admissions each year in the UK are due to ACS and more than a quarter of all deaths in the UK were due to CVDs [41]. Although the 30-day AMI mortality rate decreased from 11.9% to 8.6% between 2008 and 2017, the UK has still had a relatively high mortality rate compared to the other European countries. Furthermore, it is estimated that 4 million deaths were due to CVDs in Europe per year [42], constituting a heavy burden on the European healthcare system and economy. In addition, ACS is becoming increasingly common in developing countries such as China, Brazil and India [43, 44], with evidence suggesting ACS will become the number one killer in developing countries in the future [45].

CVD is also the leading cause of death in the United States (US), accounting for close to 1 million deaths in 2016 [46]. Being the most acute presentation of CVD, ACS accounts for approximately 13% of deaths a year in the US, with an estimated one person having a heart attack every 40 seconds according to the American Heart Association. While ACS incidence has declined in recent years, at least 1 million patients still develop ACS annually in the US [47].

2.2 COMORBIDITY

2.2.1 Definitions

In 1970, Feinstein defined the term comorbidity as "any apparent additional clinical entity that coexists or could occur in the clinical course of a patient with an index disease under study" [48]. In the countable sense of the term, comorbidity is each additional condition or disease often co-occurring with a primary condition. In general medicine, the term "comorbidity" refers to the presence of two or more distinct conditions in an individual co-existing with the primary condition of interest [49]. For example, ACS is the principal disease of hospitalisation, with diabetes and hypertension presenting at the same time. Diabetes and hypertension are the comorbidities here.

2.2.2 Impact of Comorbidity on ACS

Comorbidity is widespread in the general population with some estimates as high as a third of all patients [50]. According to a study including patients in Canada, the percentage of patients with at least one common chronic condition rose from 17.4% in 2003 to 24.3% in 2009 [51]. Another study based on 7 years of data with 212,902 patients from the Netherlands found that about 13% of the Dutch population had one or more additional chronic diseases [52].

Comorbidity is usually more chronic, severe and difficult to treat than a pure disease.

As the world's population is aging rapidly with increased life expectancy and advancements in medical care, one consequence is the increase in the number of patients living with comorbidities, particularly in the ACS population [53]. Comorbidity rarely occurs in isolation and many patients with ACS often have multiple comorbidities. In a study of temporal trends in the characteristics of AMI patients in Denmark from 1984 to 2008, it was found that the proportion of patients with very severe comorbidity increased from 3.9% to 9.6% [54].

Comorbidities may influence the prognosis of ACS patients by altering the effectiveness of treatment and the clinical course of ACS [54]. And patients' outcomes of the index disease may differ based on the type or numbers of comorbidities present [55]. It is well established that patients with a significant comorbidity burden are more likely to have adverse outcomes and are challenging to treat [56]. There have been some studies that have shown that the increasing comorbidity burden in ACS patients is related to the increased risk of death and future cardiovascular (CV) events [54, 57-59]. For example, a study with 234,331 patients with first time hospitalisation for AMI from 1984 through 2008 presented that the comorbidity burden measured five years before admission was a strong predictor of mortality within 30 days after AMI and during the remainder of the first year [54]. And another study with 715 consecutive NSTEMI patients from Jan 2004 to Dec 2005 reported higher CCI scores predicted a greater mortality risk (odds ratio (OR): 1.6, 95% confidence interval (CI): 1.4-1.8), and greater risk readmission for heart failure (OR: 1.2, 95%CI: 1.04-1.3) [59]. Comorbidities not only influence the prognosis of patients, also may also impact the choice of treatment for ACS [60]. Indeed, current international guidelines for the management of ACS recommend taking

comorbidities into account when considering treatment strategies such as invasive therapies and anti-platelet regime choices [61, 62]. A study with 740 patients with STEMI showed that the proportion of patients receiving coronary reperfusion therapy was progressively reduced with increasing chronic comorbidity from 78.8% in low comorbid group to 41.9% in high comorbid, the increased mortality in patients with comorbidities and STEMI is at least in part due to underutilization of coronary reperfusion therapy [63]. This study also showed that long-term mortality after STEMI is in part influenced by acute-phase treatment choices related to the presence of comorbidities [63].

Current clinical guidelines for the management of ACS are based on the results of trials that often exclude patients who are elderly or have a lot of comorbidities [54]. However, the number of elderly patients admitted for ACS is increasing, and elderly patients often have multiple comorbidities. Hence, incorporating the assessment of comorbidities into the prognostic assessment helps us to more accurately understand the prognosis of this population and guide our treatment choices. A study with 1017 NSTEACS patients admitted from 2002 to 2008 showed that predictive models including comorbidity scores had the highest discriminative accuracy for risk stratification after NSTEACS [64]. This result suggests that comorbidities have prognostic value for ACS patients, and the study of comorbidities may help clinicians to better risk stratify ACS patients, to adopt more targeted treatment strategies, obtain the benefits of optimal therapy to the ACS patients. Therefore, the incorporation of comorbidities in prognostic assessment has important clinical meaning.

In addition, comorbidities bring a heavy burden on the utilisation of healthcare resources. It is estimated that the care for nearly 25% of the US population who have multiple chronic conditions accounted for 65% of health care expenditure [65]. Studying the impact of comorbidities on the prognosis of

ACS patients can help to achieve better strategical management of patients and save unnecessary expenses, thereby achieving greater monetary savings.[56]

2.2.3 Measurement of Comorbidity

Comorbidities not only create difficulties for patients but also for clinicians. The decision regarding optimal treatment strategy on patients becomes complicated due to the influence of the number and types of comorbidities on the prognosis of the index disease [66]. In 1970, Alvan Feinstein pointed out that "the failure to classify and analyse comorbid conditions has led to many difficulties in medical statistics" [67]. Therefore, how to wholly evaluate the state of patients suffering from multiple comorbidities simultaneously, to assess which patient needs urgent treatments or which patient needs to be cautiously adopted invasive strategies, has become important [49, 68]. There is increasing interest in using comorbidity measures in developing risk-stratification tools in ACS patients [69].

However, how do we measure the association of comorbidities with outcomes in a given patient? Numerous comorbidity indices have been developed since no universally agreed measure or list of conditions exists to define the comorbidity burden [70]. Some of these indices attempted to standardise the "weight" or "value" of each comorbidity, and then combine all individual comorbidities weights into a total weight as a single variable for risk adjustment or to predict mortality or other outcomes, for example, the CCI/ECS comorbidity measures that would be introduced in the next section. The weight of each comorbidity in them was assigned according to the coefficient estimate associated with patient mortality in the original dataset. Researchers have verified that these tests have predictive value, but none of the tests are considered standard.

In addition, there are other measures that used individual comorbidities directly as several covariates in outcome prediction or risk-adjusted models without giving each comorbidity a different score or weight. This kind of comorbidity measure appeared in many previous articles, especially before weighted comorbidity measures were developed.

Finally, there are comorbidity measures that refer to a count of conditions, which use the number of comorbidities in a patient as a comorbidity burden score for that patient, however, this method does not reflect the effects of different comorbidity combinations or severity of comorbidities [49, 71].

2.2.4 Commonly used Comorbidity Measures

In recent years, some score-based comorbidity measures have been developed including the Charlson comorbidity index (CCI) [72] and Elixhauser comorbidity score (ECS) [73]. These two comorbidity measures are well-validated measures of comorbid burden, and both have been widely used for risk assessment in patients with ACS.

CCI was developed by M.E. Charlson in 1987 and used to assess prognosis in patients and is one of the most widely studied comorbidity indices. It is based on a point scoring system (0 to 30) for the presence of 19 related comorbidities which have been selected and assigned a weighted score according to the association of this comorbidity with 1-year all-cause mortality in the original cohort [72]. In the original CCI paper, to simplify the system, conditions with a relative risk of $1.2< \beta <1.5$ were assigned a weight of 1; conditions with a risk of $1.5< \beta < 2.5$ had a weight of 2; conditions with a relative risk of $2.5 < \beta < 3.5$ had a weight of 3; and the conditions with relative risks of 6 or more were assigned a weight of 6. This is how CCI scores were generated (the relative risks were calculated from the beta coefficients generated by the

stepwise backward proportional hazards model). Then, the CCI score (continuous) was created based on this weight system by summing all individual weights into a total score. The CCI score variable (categorical) was stratified according to the severity of comorbidity burden into 4 groups: "0" (no comorbidity), "1" (mild comorbid burden), "2" (moderate comorbid burden), "≥3" (severe comorbid burden).

CCI has been adapted by Deyo et al. (Charlson-Deyo index) for use in administrative datasets in 1992, modified to 17 categories and in combination with age [74]. It forms an age-combination index by adding a point for every 10 years of age for patients over 50 years old. There are other versions of CCI [75, 76], with the Deyo version of the CCI score being the most widely used, which is also the main version of CCI in this thesis. The CCI is a means of quantifying the prognostic impact of comorbid conditions on the basis of their number and individual impact, which has been shown to predict mortality and morbidity in patients with a variety of medical conditions [77, 78]. The characteristics and advantages of the CCI are its simplicity and ease of use compared with previous methods, and the ability to incorporate the patient's age, as well as providing a prognostic assessment of the patient's mortality rate. However, the CCI also has some drawbacks such as not considering the severity of comorbidities of many diseases (except the liver disease where it differentiates between mild, moderate and severe disease) [79].

In the same timeframe as the modified CCI index, Elixhauser et al. developed a new measure to define comorbidity as "the clinical condition of the patient before admission, as it is not related to the index cause for hospitalisation and is likely to be the important factors impacting hospital mortality and resource use" [73]. The original ECS included 30 comorbidities and was developed by Elixhauser and his colleagues in 1998 to predict the

length of stay, hospital charges, and in-hospital mortality [73]. Then, it was developed with 31 categories by Garland et al. in 2012 [80]. In 2009, a weighting algorithm was developed by van Walraven et al. based on the association between comorbidity and hospital death to modify the Elixhauser comorbidity system into a single numeric score for use in administrative data [81]. This process was undertaken using a logistic regression model with in-hospital death as the outcome variable and all 30 Elixhauser comorbidities as covariate variables. Comorbidities whose correlation coefficients exceeded 0.5 with a 95% CI exceeding 0 were considered strongly correlated with outcomes. The weights assigned to each Elixhauser comorbidity equalled its regression coefficient divided by the coefficient in the model with the smallest absolute value. Then, this quotient was rounded to the nearest whole number. ECS score variable for each patient was then calculated by summing up the points of all Elixhauser comorbidities for which they had been coded. Then, according to the method of categorisation in the Elixhauser paper, total ECS was stratified into 5 groups for the purpose of analysis: <0, 0, 1-5, 6-13, ≥14.

The modified ECS comprises 30 diseases and is a well-validated measure of comorbidity using administrative datasets. In the comparisons between the CCI and ECS indices, studies have found that the ECS index shows a better predictive performance of mortality risk [82-84]. However, the CCI method may still be a useful tool in many studies because it provides weighted scores. Meanwhile, both comorbidity measures have been shown to strongly predict complications and death in hospitalised adults, indicating the importance of comorbidity as a predictor of patient outcomes [54, 60, 84, 85].

The scoring systems of Charlson/Deyo Charlson/Elixhauser comorbidity measures are compared in **Table 2.1**.

Table 2.1: The scoring systems of Charlson/Deyo-Charlson/Elixhauser comorbidity measures.

Charlson Index	**Score**	**Charlson-Deyo Index (Deyo et al.)**	**Score**	**Elixhauser Index (van Walraven et al.)**	**Score**
Previous Myocardial infarction	1	Previous Myocardial infarction	1		
Congestive heart failure	1	Congestive heart failure	1	Congestive heart failure	7
Peripheral vascular disease	1	Peripheral vascular disease	1	Peripheral vascular disease	2
Previous Cerebrovascular disease	1	Previous Cerebrovascular disease	1		
Dementia	1	Dementia	1		
Chronic pulmonary disease	1	Chronic pulmonary disease	1	Chronic pulmonary disease	3
Rheumatologic disease	1	Rheumatologic disease	1		
Peptic ulcer	1	Peptic ulcer	1	Peptic ulcer disease, no bleeding	0
Mild liver disease	1	Mild liver disease	1		
Diabetes	1	Diabetes	1	Diabetes, uncomplicated	0
Diabetes with chronic complications	2	Diabetes with chronic complications	2	Diabetes, complicated	0
Hemiplegia or paraplegia	2	Hemiplegia or paraplegia	2	Paralysis	7
Renal Disease	2	Renal Disease	2	Renal failure	5
Any malignancy including leukaemia and lymphoma	2	Any malignancy including leukaemia and lymphoma	2	Lymphoma	9
Moderate or severe liver disease	3	Moderate or severe liver disease	3		
Metastatic solid tumour	6	Metastatic solid tumour	6	Metastatic cancer	12
AIDS/HIV	6	AIDS/HIV	6	AIDS/HIV	0

Hypertension	1	Hypertension	0
Skin ulcers/cellulitis	2		
Depression	1	Depression	3
Warfarin	1		
		Valvular disease	1
		Pulmonary circulation disorders	4
		Neurodegenerative disorders	6
		Hypothyroidism	0
		Liver disease	11
		Solid tumour without metastasis	4
		Rheumatoid arthritis/collagen vascular disease	0
		Coagulopathy	3
		Obesity	4
		Weight loss	6
		Fluid and electrolyte disorders	5
		Blood loss anemia	2
		Deficiency anemia	2
		Alcohol abuse	0
		Drug abuse	7
		Psychosis	0

2.3 SUMMARY

ACS is a common acute presentation of CVD and associated with significant morbidity, mortality and economic burden to society in the short and long term [39]. Comorbidity, defined as the coexistence of multiple conditions that co-occur with an index diagnosis at the patient level, may influence the management and outcomes of ACS patients. ACS patients appear now more likely to be living with multiple comorbidities and this has important implications for care [53]. Better evidence, obtained from large, representative samples of patients, is needed to understand how comorbidity is changing over time among ACS patients presenting to care, as well as what the relative merits are of different measures of comorbidity that can be implemented in routine practice.

Chapter 3 -
Approaches to Measuring Comorbidity and their Association with ACS outcomes

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Prognostic impact of comorbidity measures on outcomes following acute coronary syndrome: a systematic review. And the gap in evidence for this thesis.

3.1 INTRODUCTION

This chapter addresses Objective One set in section 1.2 of this thesis by summarising the existing comorbidity measurements. The findings from this chapter were published in The International Journal of Clinical Practice.

As described in the introduction chapter (2.1 & 2.2), being one of the world's leading causes of death, ACS has continuously been associated with significant morbidity, mortality and economic burden to society [39]. CVDs cause approximately one-third of all deaths in the world and ACS is a common manifestation of CVD, of which 1.8 million deaths per year are due to ACS and sudden death [86]. The death rates for CVDs have declined due to the improvement in CV prevention and ACS treatment in the last decade [46]. However, this trend might be reverting due to the world population's ageing rapidly and increase in some risk factors [86], one of the consequences is more patients live with chronic comorbid conditions, especially in those presenting with ACS [53]. As described earlier, the proportion of ACS patients with moderate to severe comorbidity burden is increasing every year [54]. International guidelines (European Society of Cardiology (ESC)) suggest that comorbidity should be considered in the decision-making processes of the management of ACS patients [87]. However, comorbidities rarely occur in isolation, with ACS patients often having multiple comorbidities such as cerebrovascular disease, diabetes and depression. When predicting the prognosis of such patients, it is necessary to consider the overall comorbidity burden of those patients, which increases the complexity of clinical decision-making in these patients [88, 89].

Therefore, how to comprehensively assess the burden status of patients with multiple comorbidities simultaneously becomes important. Since there are

no universally accepted comorbidity measures to define the overall comorbidity burden of patients, many comorbidity indices have been developed. Among them, CCI and ECS are measures of global comorbid burden and have both been widely used to predict prognosis amongst different medical conditions. Previous systematic reviews assessing the prognostic impact of comorbid burden have been restricted to CCI and reported a positive association between higher CCI scores and risk of mortality in patients with ACS [77]. However, several other studies have evaluated the prognostic value of other comorbidity measures in ACS patients with some literature indicating that ECS and other comorbidity measures might outperform CCI scores in outcome prediction [82, 83].

A variety of comorbidity measures were developed to define the overall comorbid burden of ACS patients and investigate the prognostic impact, which reflected the importance of studying comorbidity measures. However, to date, there are still no reviews conducted to identify all the existing comorbidity measures that were used in ACS patients and summarise this evidence. Hence, it is important to undertake a systematic review of the comorbidity measures in ACS patients.

3.2 OBJECTIVES

Thus, in order to address the above aim (which was also set out as the first research question in section 1.2 of this thesis), the main objectives of the systematic review in this chapter are to:

1. Identify the existing comorbidity measures or indices that have been used in ACS patients.
2. Investigate the type of comorbidity measures and how they have been used in the modelling.

3. Summarise the association between the comorbidity measures with ACS outcomes.

3.3 METHODS

The protocol used for this review has been registered in the international prospective register of systematic reviews (PROSPERO registration number: CRD42019138044). The review was conducted according to the guidance of systematic review and meta-analysis for prognostic factor studies proposed by Riley et al [90].

3.3.1 Data Sources and Searches

The bibliographic databases (MEDLINE (OvidSP), EMBASE (OvidSP)) were searched to identify all potentially relevant published studies from inception to May 2019. Web of Science was searched to identify potentially relevant unpublished abstracts from the following three conference journals: American Heart Association (AHA), American College of Cardiology (ACC) and ESC from 2017 onwards. Reference lists of all included studies were scrutinised, especially the primary studies included in the relevant systematic reviews identified from each database. Searches used broad terms and combinations of these terms that were related to the concept of three core terms: ACS, comorbidity and measure (**Appendix Table 3.1**). Search strategies combined a series of keywords with the most inclusive suffix and database-specific Medical Subject Heading terms (MeSH) with appropriate Boolean operators (**Appendix Table 3.1**). The search strategies were further refined in consultation with an internal systematic review team prior to final execution.

3.3.2 Study Selection

3.3.2.1 Inclusion criteria

Eligibility criteria were discussed and finalised by clinicians and epidemiologists. Detailed inclusion and exclusion criteria for the review are provided in **Appendix Table 3.2**.

Study design

The literature search included randomised control trials (RCTs), cohort studies, case-control studies, systematic reviews, non-systematic reviews and conference abstracts (2017 onwards only). No language restriction was imposed. Non-human articles and study design papers were all excluded.

Population of interest/outcome of interest

Selected studies were limited to patients hospitalised for an ACS. ACS was defined as either AMI (STEMI or NSTEMI) or UA. Studies with patients presenting without AMI (such as stable angina, CHD, elective PCI and angiogram) were excluded. Outcomes of interest were one of the following three with no restriction on time point of outcome measurement: 1) mortality, 2) MACCE, 3) major bleeding.

Comorbidity measures as prognostic factors

Comorbid burden of patients was measured by composite comorbidity measures (scores or indexes). The comorbidity measures could be developed based on a simple count of comorbidities or on a numerical system with weightings assigned to individual comorbidities to produce a final weighted score. Studies must report at least one comorbidity measure (score or index) with estimate effects of association between comorbidity burden and outcomes, whether comorbidity was the primary prognostic factor of interest or just another covariate in the statistical models. Studies that applied comorbidity measures in the model but did not report estimates were excluded. It was agreed

(decided by consensus of J.E., G.P. and M.A.M.) that studies only applying comorbidity measure as a confounder without estimate effects of outcomes were excluded.

3.3.2.2 Selection process

References management software (Rayyan) was used to screen the studies and record reviewer decisions. After removing duplicates, every abstract was screened independently by two reviewers (F.Z., C.W.) to eliminate irrelevant papers using pre-specified criteria based on whether papers 1) included an ACS patient population, 2) included comorbidity measures as defined above, 3) included one of the outcomes of interest (mortality, MACCE, bleeding). Then, the full texts of potential papers identified in the first step were obtained and reviewed by two independent reviewers based on the full inclusion and exclusion criteria defined above. Subsequently, any potentially relevant articles were obtained for full-text review independently by three reviewers (F.Z., C.W. and Y.C.). When the two reviewers had any discordances about whether to include or exclude a paper, they first discussed them to reach a consensus and the final study inclusion was decided by the senior authors (J.E., G.P. and M.A.M.).

3.3.3 Data Extraction and Quality Appraisal

Data extraction was completed independently by two reviewers using a pre-formatted Excel spreadsheet according to the critical appraisal and data extraction for systematic reviews of prognostic factor studies (CHARMS-PF) checklist [90, 91]. CHARMS-PF is suitable for data extraction in reviews of prognostic factors and it was modified based on the original CHARMS checklist which is for data extraction in the systematic reviews of prediction modelling studies. I contacted the authors of included studies where necessary data was missing or methodological information was not clear. Information collected from

the studies includes the authors, year of publication, country, study design, study population, patient characteristics, sample size, the database used, outcomes, design of comorbidity measures, variables included in comorbidity measures, modelling method and how comorbidity measures were included in the model (continuous or categorical), the association between comorbid burden and outcomes, prognostic effect estimates and their CIs, adjustment factors used, if validated or not, and summary of main findings.

Quality assessment of the studies was performed using the Quality In Prognostic factor Studies (QUIPS) checklist [92, 93]. This tool was originally developed in 2006 and refined by Hayden and colleagues in 2013 for systematic reviews of prognostic factor studies by examining risk of bias (RoB) across the following six domains: study participation, study attrition, prognostic factor measurement, outcome measurement, adjustment for other prognostic factors and statistical analysis and reporting. Each of the 6 domains includes several prompting items, which were taken together to obtain the judgement of risk of bias in each domain (high, moderate or low RoB). The method used to determine the overall risk of bias for each study was described by Grooten et al. [93]: a study having six low RoB or only having one moderate RoB was classified as low RoB (green); if more than one domain were assessed as high RoB, or ≥3 moderate RoB, then this article was treated as high RoB (red); the remaining papers in between were considered as moderate RoB (yellow). Three reviewers independently completed this assessment, and the final decisions were reviewed and made by the senior authors.

3.3.4 Data Synthesis and Analysis

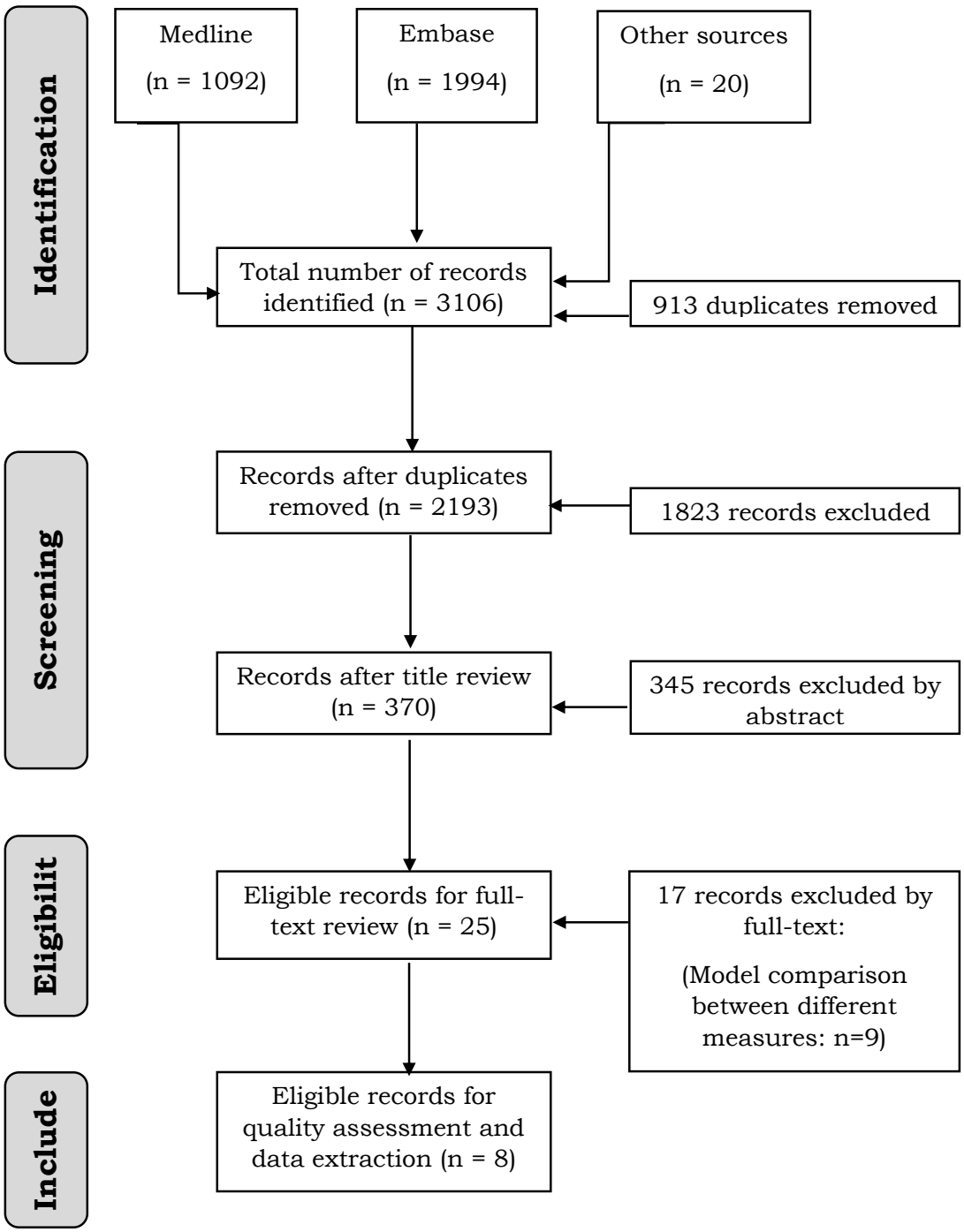
A narrative synthesis was conducted instead of implementing a meta-analysis, due to the heterogeneity related to the length of follow-up, modelling

used, how the comorbidity measure was modelled, adjustment variables used, and ACS presentation. Data was summarised across studies and interpreted by 1) describing the characteristics of the included studies, 2) determining the design of comorbidity measures used to define the comorbid burden and identifying how comorbidity measures were coded in the model, 3) synthesising the association between comorbid burden and ACS outcomes and the prognostic effect sizes.

3.4 RESULTS

A total of 3106 studies were retrieved from the search. After excluding studies that did not meet the inclusion criteria, a total of one retrospective study [54] and seven prospective studies [59, 60, 63, 64, 94-96] were included (**Figure 3.1**). In addition, another nine studies were identified [82, 83, 97-103] that did not report any prognostic impact of comorbidity measure on ACS outcomes however offered information on model comparison in terms of predictive performance of different comorbidity measures.

Figure 3.1: Screening flowchart of articles for the systematic review.



3.4.1 Characteristics of Included Studies

The study design and cohort characteristics of each included paper are presented in **Table 3.1**. The only retrospective study had a follow up of 24 years, and the remaining seven prospective studies had follow-up duration between one year and ten years. All the studies were conducted between 1984 and 2008 and published between 2004 and 2019. The majority of the studies were conducted in European countries including four from Spain [59, 60, 64, 95], one from Italy [63], one from Denmark [54] and one from Switzerland [96], with the exception of one from Israel [94]. Most studies were published as a research article although one was published as an abstract. There was no age limitation in most studies except one study with an age limit of 15 years old or higher and one study which focused on patients aged ≥65 years.

This review included a total of 270,263 patients with the sample size of individual studies ranging from 740 to 234,331 patients. The study populations comprised patients with ACS (N=29,620 in one study [96]), those with AMI (total N= 237,251 in three studies), those with NSTEMI (total N=2652 in three studies), and those with STEMI (N=740 in one study [63]). The mean ages ranged from 66 to 74 years old from studies which reported such data. The percentages of female patients varied between 27% and 42%.

Table 3.1: Study design and characteristics of the included studies.

Study ID	Study design; Year; Country	Study population size; type of population	Age (median, mean ± SD, %)	Female (%)	Description of inclusion for participants
Schmidt 2012 [54]	Retrospective cohort study; 1984-2008; Denmark	234,331 AMI	Women: median 74 in 1984 to median 77 in 2008; Men: median 68	37.9%	All first-time hospitalisations for MI among Danish-born inhabitants aged 15 years or older.
Plakht 2010 [94]	Prospective cohort study; 2002-2004; Israel	1,885 AMI	<65, 44.6% 65-75, 26.3% >75, 29.1%;	31.6%	No age limitation. Patients who had been admitted with AMI and discharged alive from hospital.
Sanchis 2019 [95]	Prospective cohort study; 2002-2008 and 2010-2012; Spain	920 non-ST-elevation acute coronary syndrome (NSTEACS)	76.4 ± 7.0	42%	Elderly (≥65) patients admitted for NSTEACS.
Balzi 2005 [63]	Prospective cohort study; 2000-2001; Italy	740 STEMI	69.5 ± 12.2	30.1%	No age limitation. All residents in the Florence area arriving alive to the emergency department of 1 of the 6 hospitals with a suspected STEMI.

Study ID	Study design; Year; Country	Study population size; type of population	Age (median, mean ± SD, %)	Female (%)	Description of inclusion for participants
Sanchis 2011 [64]	Prospective cohort study; 2002-2008, Spain	1017 NSTEACS	68 ± 13	34%	No age limitation. The patients who admitted to the Hospital with NSTEACS.
Núñez 2004 [60]	Prospective cohort study; 2000-2003; Spain	1035 AMI (508 STEMI, 527 NSTEMI)	68 ± 3	32.1%	No age limitation. Patients diagnosed with AMI who were admitted to hospital.
Ramirez-Marrero 2011 [59]	Prospective cohort study; 2004-2005; Spain	715 NSTEACS	66.2 ± 11.2	NA	No age limitation. Patients admitted to hospital for NSTEACS.
Radovanovic 2014 [96]	Prospective cohort study; 2002-2012; Swiss	29,620 ACS	66.3 ± 12.8	27%	No age limitation All ACS patients. ACS included acute MI and unstable angina.

SD: stand deviation; AMI: acute myocardial infarction; MI: myocardial infarction; NSTEACS: non-ST-segment elevation myocardial infarction; STEMI: ST-elevation myocardial infarction; NA: not available; NSTEMI: non-ST-elevation myocardial infarction; ACS: acute coronary syndrome.

3.4.2 Quality Assessment of Included Studies

Risk of bias assessment based on the QUIPS tool showed that six studies [59, 60, 63, 64, 94, 95] were at high RoB (see **Figure 3.2**) mainly due to lack of information on "study attrition, prognostic factor measurement, statistical analysis and reporting" domains (e.g., no information on response rate for study participants, no description of patients who dropped out, methodological issues, or selective reporting of results). Only the studies from Schmidt et al [54]. and Radovanovic et al. [96] were evaluated as low RoB and moderate RoB respectively. Four studies were at low RoB in the "outcome measurement" domain, whilst more than half of studies were at low RoB in "study participation and study confounding" domains.

3.4.3 Characteristics of Identified Comorbidity Measures

The details of the comorbidity measures' design, reported outcomes, modelling used and the association of comorbid burden with ACS outcomes across the included studies were summarised in **Table 3.2**.

Figure 3.2 Risk of bias for the included studies according to the QUIPS tool.

	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Statistical Analysis and Reporting	Overall Risk of Bias
Schmidt 2012							
Plakht 2010							
Sanchis 2019							
Balzi 2005							
Sanchis 2011							
Núñez 2004							
RamirezMarrero 2011							
Radovanovic 2014							

Low risk (green); moderate risk (yellow); high risk (red).

Table 3.2 Summary of measured outcome, comorbid measures used, modelling used, association presented and effect characteristics.

Study ID	Outcomes	Comorbidity measure used	prognostic factor/covariate; type of variable	Modelling	Final prognostic effect estimates for comorbidity measure (unadjusted and adjusted by other covariates)
Schmidt 2012	30-day all-cause mortality, 31-365 days all-cause mortality	The original CCI (19 conditions)	CCI as prognostic factor. Summary scores as a categorical variable (0, 1, 2, ≥3)	Cox proportional hazard regression	<u>30-day mortality:</u> Results from unadjusted models: 1 vs 0: HR=1.85 (95%CI: 1.73-1.98) 2 vs 0: HR=2.09 (95%CI: 1.94-2.25) ≥3 vs 0: HR=2.72 (95%CI: 2.53-2.91) Results from adjusted models: 1 vs 0: HR=1.35 (95%CI: 1.26-1.45) 2 vs 0: HR=1.52 (95%CI: 1.41-1.64) ≥3 vs 0: HR=1.96 (95%CI: 1.83-2.11) <u>31-365-day mortality:</u> Results from unadjusted models: 1 vs 0: HR=2.64 (95%CI: 2.42-2.87) 2 vs 0: HR=3.61 (95%CI: 3.30-3.96) ≥3 vs 0: HR=5.80 (95%CI: 5.34-6.31) Results from adjusted models: 1 vs 0: HR=1.83 (95%CI: 1.68-2.00) 2 vs 0: HR=2.50 (95%CI: 2.29-2.74) ≥3 vs 0: HR=3.89 (95%CI: 3.58-4.24)
Plakht 2010	1-year all-cause mortality	SAMI (11 parameters)	SAMI as prognostic factor. Summary scores as a continuous variable	Logistic regression	Results from adjusted models: OR=1.39 (95%CI: 1.33-1.45)

Study ID	Outcomes	Comorbidity measure used	prognostic factor/covariate; type of variable	Modelling	Final prognostic effect estimates for comorbidity measure (unadjusted and adjusted by other covariates)
Sanchis 2019	1-year all-cause mortality	SCM (6 comorbidities)	SCM as prognostic factor. Summary numbers of comorbidities as a categorical variable (0-1, 2, ≥3)	Cox proportional hazard regression	No results from unadjusted models. Results from adjusted models: 2 vs 0-1: HR=1.29 (95%CI: 0.81-2.04) ≥3 vs 0-1: HR=1.91 (95%CI: 1.20-3.03)
Balzi 2005	1-year all-cause mortality	CS (14 chronic diseases)	CS as a covariate. Summary scores and tertile to 3 categories (cut-off values can vary)	Cox proportional hazard regression	No results from unadjusted models. Results from adjusted models: 2 vs 1: HR=1.87 (95%CI: 1.04-3.38) 3 vs 1: HR=2.12 (95%CI: 1.18-3.82)
Sanchis 2011	1-year all-cause mortality	SCI (5 comorbidities)	SCI as prognostic factor. Summary points as a categorical variable (0, 1-2, ≥3)	Cox proportional hazard regression	No results from unadjusted models. Results from adjusted models: 1-2 vs 0: HR=1.7 (95%CI: 1.0-3.1) ≥3 vs 0: HR=4.8 (95%CI: 2.7-8.5)
Núñez 2004	30-day mortality or reinfarction, 1-year mortality or reinfarction	CCI/Deyo (17 comorbidities)	CCI as prognostic factor. Summary scores as a categorical variable (0,1,2, ≥3)	Cox proportional hazard regression	<u>30-day mortality or reinfarction:</u> No results from unadjusted models. Results from adjusted models: 1 vs 0: HR=1.69 (95%CI: 1.10-2.59) 2 vs 0: HR=1.78 (95%CI: 1.08-2.92) ≥3 vs 0: HR=1.57 (95%CI: 0.87-2.83) <u>1-year mortality or reinfarction:</u> No results from unadjusted models. Results from adjusted models:

Study ID	Outcomes	Comorbidity measure used	prognostic factor/covariate; type of variable	Modelling	Final prognostic effect estimates for comorbidity measure (unadjusted and adjusted by other covariates)
					1 vs 0: HR=1.62 (95%CI: 1.18-2.23) 2 vs 0: HR=2.00 (95%CI: 1.39-2.89) ≥3 vs 0: HR=2.24 (95%CI: 1.50-3.36)
Ramirez-Marrero 2011	Intrahospital-phase mortality, Long-term (24-month) mortality, readmission for HF after follow-up, MACEs during follow-up	CCI (unknown version)	CCI as prognostic factor. Summary scores as a continuous variable	NA	Unclear whether the results are from unadjusted or adjusted models: Intrahospital- phase mortality: OR=1.6 (95%CI: 1.4-1.8) Long-term (24-month) mortality: OR=1.3 (95%CI: 1.2-1.5) readmission for HF: OR=1.2 (95%CI: 1.04-1.3) MACESs during follow-up: OR=1.1 (95%CI: 1-1.2)
Radovanovic 2014	In-hospital mortality, 1-year mortality	The original CCI (19 conditions)	CCI as prognostic factor. For in-hospital mortality: Summary scores as a categorical variable, For 1-year mortality: Summary scores as a continuous variable	Logistic regression	In-hospital mortality: No results from unadjusted models. Results from adjusted models: 1 vs 0: OR=1.36 (95%CI: 1.16-1.60) 2 vs 0: OR=1.65 (95%CI: 1.38-1.97) ≥3 vs 0: OR=2.20 (95%CI: 1.86-2.57) 1-year mortality: No results from unadjusted models. Results from adjusted models: OR=1.44 (95%CI: 1.36-1.53)

CCI: Charlson comorbidity index; HR: hazard ratio; CI: confidence interval; SAMI: Soroka acute myocardial infarction; OR: odd ratio; SCM: simplified comorbidity measure; SCI: simple comorbidity index; CS: chronic comorbidity score; HF: heat failure; MACE: major acute cardiovascular events; NA: not available; ECS: Elixhauser comorbidity score; MACCE: major acute cardiovascular and cerebrovascular events.

3.4.3.1 Comorbidity measures' design

A total of five different types of comorbidity measures were identified in the studies examined: 1) CCI, 2) Soroka Acute Myocardial Infarction (SAMI), 3) Simplified comorbidity measure (SCM), 4) Chronic comorbidity score (CS), 5) Simple comorbidity index (SCI). These comorbidity measures assessed the comorbid burden using various approaches such as 1) summarising weighted scores of each condition into severity categories or into a numerical score, 2) counting the number of comorbidities into a categorical or numerical variable. All identified comorbidity measures' details are summarised in **Appendix Table 3.3**.

CCI

The CCI is a scoring system that developed weights for each condition based on the adjusted relative risk (RR) of one-year mortality and has been broadly validated for other groups of patients such as acute and chronic ischaemic heart disease patients. It was developed by Mary Charlson and colleagues in 1987 [72], which originally consisted of 19 conditions and was modified into 17 categories in 1992 by Deyo et al [74]. The CCI was the most widely used measure in this review with four studies [54, 59, 60, 96] using CCI to define comorbid burden, with two presenting the use of the original CCI score rather than the Deyo modification. Three of these studies computed CCI scores for each patient and categorised the scores into four levels of comorbidity (CCI=0, 1, 2 or ≥3), whereas the study by Ramirez-Marrero applied CCI scores as a continuous variable.

SAMI

The SAMI risk score was developed in a study [94] and internally validated in 2010 using data (n=1885 AMIs for development, n=888 AMIs for

internal validation) obtained from the same population in Israel from 2002 to 2004. It comprised 11 parameters (see **Appendix Table 3.3**) derived from a variety of traditional CV and non-CV comorbidities, every parameter corresponds to a weight which was based on their associations with 1-year mortality and ranged from -6 to 4. The total score for each patient was calculated to define comorbid burden and used as a continuous variable in the model.

SCM

The SCM was produced in one study in 2019 using the data from the cohorts of elderly (≥65 years old) patients in Spain (n=920 NSTEMIs), which consists of six conditions. It was used as a categorical variable with three levels (SCM=0-1, 2, ≥3) to define the comorbid burden according to the number of the six comorbidities [95].

CS

The CS measure was developed from medical history in a study published in 2005 (n=740 STEMIs, between 2000 and 2001). It contains 14 chronic diseases that were assigned a disease-specific score based on the strength (ln(hazard ratios (HR))) of their impact on 1-year mortality. A summary CS was computed for each patient by summing disease-specific scores and then divided into a categorical variable with three levels (from CS-1 to CS-3) with increasing comorbid burden [54]. The difference of the CS with other measures was its scores all contained decimal points and the way of grouping was according to the CS tertiles which would vary in different populations.

SCI

The SCI was created from an NSTEMI population (n=1017, between 2002-2008) in 2011 using five comorbidity variables that were independently associated with the 1-year mortality by assigning 1 or 2 points according to the weight of their HR. One study [64] stratified patients by summing the total SCI

scores into three groups: SCI=0, 1-2, ≥3.

3.4.3.2 Reported outcomes and modelling used

The clinical outcomes among the eight studies were diverse with the most frequently reported being mortality at various follow-up periods. One-year all-cause mortality was commonly used in six studies. Other less frequent outcomes in individual studies included: in-hospital mortality, 30-day mortality, and 2-year mortality. The modelling approaches used to assess the association of comorbidity measures with clinical outcomes were cox proportional hazard regression identified in five studies and logistic regression identified in two studies, no information was reported in the study by Ramirez-Marrero (**Table 3.2**).

3.4.3.3 Synthesising the association of comorbidity measures with reported outcomes

Overall, the associations reported (ORs and HRs, in **Table 3.2**) between comorbidity measures and clinical outcomes indicated patients in a higher comorbid group or with higher scores were associated with a higher risk of adverse events. For example, five studies that treated comorbid burden as categorical and reported long-term mortality (≥ one year), indicated the adjusted HRs of the highest comorbid group (vs the reference group) ranged from 1.9 to 4.8 (95% CIs located between 1.2 and 8.5); for 30-day mortality, two studies suggested the adjusted HRs of the highest comorbid group ranged from about 1.6 to 2 (95% CIs from 0.8 to 2.8). In studies using logistic regression models with long-term mortality, three studies that treated comorbidity scores as continuous variables reported ORs between 1.3 and 1.44 (95% CIs from 1.2 to 1.53) per one-unit increase in score. For in-hospital mortality, one study [59] that used CCI scores as a continuous variable reported that higher comorbid

burden was associated with greater mortality risk (OR 1.6, 95%CI, 1.4-1.8), whilst one study [96] that used CCI scores as a categorical variable reported that the highest comorbid group had an adjusted OR of 2.2 (95%CI 1.86-2.57) for in-hospital mortality compared to the reference group. In addition to other outcomes, one study [59] reported the associations of major acute cardiovascular events (MACE) (OR 1.2, 95%CI, 1.04-1.3) and readmission for ACS (OR 1.1, 95%CI, 1-1.2) with CCI scores used as continuous variables where the estimates also indicated patients with a heavier comorbid burden, were more likely to sustain events. Most studies reported adjusted estimates of the association between CCI score and outcomes while only one study [54] reported unadjusted estimates and the study by Ramirez-Marrero lacked information on whether the models were adjusted or unadjusted.

3.4.4 Studies that only Reported Model Comparison

Nine studies were identified that only reported model comparisons using various comorbidity measures in ACS patients. Although these studies did not have the intended prognostic results for this review as per the protocol, their findings on performance comparison are relevant to the review. The details are presented in **Appendix Table 3.4**.

All nine studies were published between 1994 and 2014. Retrospective study design was present in seven studies [83, 97-101, 103] while a prospective design was identified in one study [82] and a historical inception cohort design was used in the remaining study [102]. The study population comprised mainly patients with AMI (N=382,324 in eight studies) and participants with ACS (N=1202 in one study), while the sample size ranged in the individual studies between 1202 and 162,299. Seven comorbidity measures were mentioned in the studies: the original ECS; CCI (four different adaptions: (Deyo, Romano, Dart-

mouth-Manitoba, D'Hoore); the Centre for Medicare and Medicaid Service-Hierarchical Condition Categories model (CMS-HCC); the Ontario AMI prediction rule model (OAMIPR); the Global Registry of Acute Coronary Events risk prediction index (GRPI); and two measures in the same study named C_{ADM} index and C_{DISCH} index, respectively. With different comorbidity measures as prognostic factors, the performances of logistic regressions were assessed and compared. Of seven measures, the most common measures were CCI (eight studies) and ECS (six studies), which were also frequently compared and indicated that ECS outperforms CCI in these studies. In-hospital mortality was the main outcome in most studies. All the studies employed C-statistic as the method to assess and compare model performance. Five studies considered one or two additional methods including calibration slope, Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), Nagelkerke R-square, and G-square statistic.

3.5 DISCUSSION (GAP IN THE EVIDENCE FOR THIS THESIS)

The aim of the present review was to provide an overview of existing measures used to evaluate comorbid burden in patients with ACS and investigate the prognostic impact of different measures of a comorbid burden on ACS outcomes. It reports that the most widely studied comorbidity measure used to investigate the relationship between comorbid burden and outcomes in patients with ACS is CCI. It was found that a greater comorbidity burden irrespective of how it was measured/defined was consistently associated with an increased risk of a variety of ACS outcomes including mortality and MACCE. Finally, this review also observed model comparisons using different comorbidity measures which implied ECS might have better performance than CCI.

3.5.1 Summary of Included Studies

This review is the first analysis to study the prognostic impact of a broad range of comorbidity measures in patients with ACS. The eight identified studies, dated between 2004 and 2019, represents data derived from over a quarter of a million patients from diverse healthcare systems with a broad range of comorbidity measures used. Many of the identified comorbidity measures except the CS [63] have been externally validated, for example, CCI was described in a general medical population and has been validated extensively in a number of medical conditions [72, 74, 104].

Nonetheless, there were drawbacks to these studies. Several studies had selective reporting of results, thereby increasing the difficulty of quality assessment as important information was either omitted or unclear (e.g., missing data, adjustment variables) [92]. Meanwhile, many of the comorbidity scores were created early using historical datasets with small sample sizes, where the prognostic impact of particular comorbidity may have been only relevant to the population studied. As patterns of medical diagnosis and treatments evolve, the estimated magnitude and direction of association between comorbidity and adverse outcomes may change. For example, AIDS is scored as +6 points in the CCI score consistent with the poor outcomes of AIDS when the CCI score was developed, even though the longer-term outcomes of patients with AIDS have substantially improved in contemporary clinical practice [105]. In addition, most identified measures apart from CCI have been merely validated in specific populations and may not be suitable for the assessment of prognosis in other groups of patients more widely. Finally, this review showed ECS was not used widely to investigate the association of comorbidity burden with ACS outcomes, even though comparative studies suggest that it may be superior in predicting mortality in CV cohorts [82, 83].

Previously a meta-analysis [77] has summarised the impact of CCI scores on CVDs, which showed that a higher CCI score was associated with an increased risk of mortality in ACS patients, with each unit increase of CCI score associated with a 33% increased risk of mortality (RR 1.33, 95% CI 1.15-1.54). While this review quantifies the association of CCI scores with ACS outcomes in a larger number of studies, this analysis provides more granular insights into the impact of other comorbidity measures on ACS-related outcomes and highlighted that regardless of how it was defined, a higher comorbidity burden was associated with an increased risk of mortality or MACE. For example, NSTEACS patients with the highest comorbid burden (SCI≥3) had an adjusted HR of 4.8 (95%CI: 2.7-8.5) for one-year mortality compared to those with no comorbidities (SCI=0) [64]. Another study using CCI score as a continuous variable also showed NSTEACS patients with a higher comorbidity burden (CCI>0) were more likely to encounter MACE (OR 1.2, 95%CI, 1.04-1.3) [59].

There are several reasons why ACS patients with a greater comorbidity burden have an increased risk of adverse outcomes. A study [96] found that the higher the comorbid burden, the longer the delay between the symptom onset and admission. Besides, the symptoms were less typical and there was a higher degree of haemodynamic instability which translated into a higher Killip class. The 6-month mortality of ACS patients with Killip class I vs class III/IV is around 4-5% vs 23-28% [106, 107]. An important therapeutic goal in AMI is rapid coronary reperfusion and current guidelines recommend early routine invasive management particularly for STEMI (in the form of primary PCI) and high-risk NSTEMI presentations [63]. However, as highlighted by Sachis et al, invasive strategies are underused in comorbid patients in the context of ACS. The most consistent finding across the studies identified in this review was the lower rate of utilisation of coronary reperfusion therapy (e.g., PCI or

thrombolysis) among ACS patients with higher comorbidity. For example, Balzi et al found that the proportion of patients receiving coronary reperfusion therapy reduced as the comorbidity increased, from 78.8% in the group with the least comorbidity to 41.9% in the group with the most comorbidities. This phenomenon may be attributed to the perception that patients with high comorbidities do not benefit from invasive management or are poor candidates for revascularization. Furthermore, there is evidence that comorbid patients undergoing coronary revascularization with PCI are at greater risk from sustaining major bleeding complications and adverse outcomes [78, 108, 109]. However, data does not support such a conservative approach to such patients, for example, a study with 698 AMI patients using data from the Florence 2 registry in Italy between 2008 and 2009 demonstrated that coronary reperfusion was associated with a better prognosis (one-year mortality) than conservative therapy and the differences were more marked with increasing comorbid scores [110]. Furthermore, in the sensitivity analysis conducted by Sanchis et al, in-hospital revascularization reduced mortality in both groups of patients with less than three comorbidities and patients with three or more comorbidities, with the magnitude of mortality reduction was greater among more comorbid patients (20.3% vs 10.0%).

3.5.2 Summary of Comparison Studies

Among the model comparison studies, studies report that ECS might perform better than the more widely used measure, CCI in prediction models for ACS-related outcomes. For example, a retrospective study of 144,687 AMI patients using administrative data from five countries in 2008-2009 reported that ECS may achieve better discrimination than CCI in the prediction of 30-day mortality [82]; another two retrospective studies with a total of 50,479 AMI

patients from 1994 to 2001 in California and Canada demonstrated the same conclusion in predicting in-hospital mortality. A study with 8,961 AMI patients in 2001-2002 demonstrated the ECS model had the largest C-statistic (best-discriminated ability) in predicting one-year follow-up mortality [97]. It is noted that four studies that included ECS applied it as separate binary variables in the model rather than using its scoring system due to lack of the weighting algorithm of the original ECS. Meanwhile, those studies also used CCI comorbidities as individual categorical variables instead of their weights that were more commonly used in practice. It is possible this way could cause ECS to have better predictive performance than CCI as ECS contained more conditions than CCI. Whilst ECS may have better discrimination than CCI, it is more complex to calculate than CCI, so the use of such comorbidity scores in clinical practice is often a balance between usability and performance.

3.5.3 Limitations

It is the first review to study the prognostic impact of a broad range of comorbidity measures in patients with ACS. This analysis was performed complying with updated guidance [90] of the systemic review for prognostic factor studies, every step of screening was independently conducted by at least two reviewers. Meanwhile, according to the CHARMS-PF checklist [91], which is an improved version of guidance for data extraction of prognostic factor study, the data was extracted independently by at least two reviewers. However, it was also acknowledged the limitations of this review. It only has a small number of studies included, with most of them considered to be at high RoB based on the assessment of QUIPS. Owing to the heterogeneity of these studies, with substantial differences in modelling approaches, ACS outcomes and coding of comorbidity variables, quantitative synthesis was not performed.

3.5.4 Implications for Future Research

It is well known that comorbidities are associated with the prognosis of ACS patients. From this review, it can be found that the current literature has several limitations, which are summarized as follows:

I. In the past decade, the demographics and comorbidity burden of ACS patients have changed significantly. Studies identified in this review illustrated the rising burden of co-existing comorbidities in ACS patients. However, there is still limited data regarding the epidemiological changes in demographics, risk profile and comorbidity burden of ACS patients over the past decade, especially the data using the commonly used comorbidity measures in recent years, such as CCI and ECS. As mentioned above, most current research results regarding the changes of demographics and risk profiles in different comorbidity burden subgroups of patients were limited to old datasets with small sample sizes. Except for one study that used CCI had a long time span dataset, other studies that used CCI also presented the above drawbacks. Therefore, the future research will study the temporal trend of the baseline characteristics, the burden of comorbidities, the use of treatment strategies, and the prognostic outcomes of ACS patients between the recent 11 years using a nationwide database in the US. I will also investigate the changes in those characteristics in different risk subgroups of ACS patients based on the two most commonly used comorbidity measures.

II. According to the ESC guideline, comorbidity burden needs to be considered in predicting the prognosis of ACS patients and risk

adjustment [111]. It can be seen in this review that many measures for the definition and measurement of patient comorbidity burden have emerged. However, as aforementioned, most identified measures apart from CCI were not suitable for the assessment of prognosis in other populations more widely apart from the dataset they used to develop the measures. Even in the studies with the use of CCI, they still had limitations as described early. Additionally, during the screening of included studies, it was found that most studies only considered a few individual common comorbidities of patients rather than developed comorbid measures [112], which might lead to bias in prediction since those studies did not consider the degree of impact of different comorbidities on patient prognosis. Plus some studies that used CCI did not focus on the prognostic impact of comorbidity burden in ACS patients [113]. In addition, this review found ECS was not used widely to investigate the prognostic impact of comorbidity burden on ACS outcomes. Based on the above, data is still limited about the prognostic impact of comorbid burden defined by widely used comorbidity measures (CCI or ECS) on ACS patients and the receipt of invasive strategies. Therefore, it is important to study the association between the comorbidity burden defined by the widely accepted and used comorbidity measures and the prognosis of ACS patients or the use of invasive strategies, thus benefit the guidance to management strategy and reliably assessing prognosis at an individual patient level.

III. Although the ESC guideline recommends the importance of comorbidity burden in the prognostic study of ACS patients, there is no specific and clear explanation on the definition of comorbidity burden, also no specification on which comorbidity measures is more beneficial in

predicting the outcome of ACS patients or risk stratification. So far, although some comparison studies [82, 83, 99] identified in this review indicated that the Elixhauser method outperformed in the prediction of outcomes following ACS than the Charlson/Deyo method, they all had their own limitations and the conclusions reached were also divided. For example, when compared CCI and ECS, even though the CCI scoring system was widely used in practice, many studies applied them as separate binary variables in the model rather than using their scoring system due to the lack of the weighting algorithm of the original ECS, which may result in ECS having better predictive performance than CCI because ECS contains more conditions than CCI [114]. Therefore, the subsequent research will use the scoring systems of these two widely accepted comorbidity measures to define the patient's comorbidity burden and compare their performances in predicting ACS outcomes using a national dataset, so as to provide a reference for clinical decision-making.

IV. In addition, although there have been some studies to compare the CCI and ECS measures, there is currently no research investigating whether these two measures identify the same groups of patients as being comorbid at the same level or whether they identify different groups of patients within the population. Meanwhile, there is no data around the level of agreement between these two measures of comorbidity burden. Therefore, it is essential to investigate how the agreement between these comorbidity methods is when classifying patients. Potential research will aim to explore a comprehensive examination of the agreement between these two different comorbidity measures in ACS patients and investigate the potential reasons for it, for instance, the same individual

comorbidities having different weighting scores in these two measures might cause the difference in the grouping results.

In summary, the main rationale for this thesis is to investigate the prognostic impact of the comorbidity burden with ACS outcomes and the receipt of treatments, find out which comorbidity measure provided more prognostic values and what degree of agreement they achieve between each other.

In order to achieve these goals and fill the current gap in the evidence, the thesis will start from the following aspects: Chapters 5 and 6 will explore the temporal trends in comorbidity burden and impact on prognosis in patients with ACS using both CCI and ECS; Chapter 7 will compare the performance of CCI and ECS in predicting ACS outcomes, Chapter 8 will present the agreement analysis between CCI and ECS.

3.6 CONCLUSION

This systematic review paper identified five comorbidity measures, summarised their associations with ACS outcomes and assessed the quality of those studies. It was observed that CCI was the most widely used measure of comorbidity burden that was used to explore the relationship between comorbidity burden and ACS outcomes. Despite methodological heterogeneity among the identified studies, the review confirmed that irrespective of how comorbidity burden was defined, higher comorbidity burden or scores were associated with a greater risk of mortality and MACE in patients presenting with ACS. The addition of measures of comorbidity burden may help to optimise risk stratification tools used in clinical practice to guide treatment for patients with ACS.

Chapter 4 - Data Source

Description of data source and preliminary data processing.

4.1 INTRODUCTION

This chapter describes the database used in this thesis. The source of the dataset, data structure in the dataset, sampling means, changes of design in the dataset, data elements contained in the dataset, type of coding system, strengths and limitations of the dataset, appraisal of data source and relevant guidelines and so on are all introduced. Then, the preliminary work on the dataset including data linking, data manipulation and data cleaning is described. As every chapter in this thesis has its own objective and study design, the dataset will be further processed to fit each chapter's goal. Full of details of methods will be described specifically in the corresponding chapters.

4.2 DATA SOURCE FOR THIS THESIS

The database used in this thesis is called National (Nationwide) Inpatient Sample (NIS), which is the largest publicly available all-payer inpatient health care databases in the US. The NIS is a part of the Healthcare Cost and Utilization Project (HCUP), which is sponsored by the Agency for Healthcare Research and Quality (AHRQ) [115], HCUP data inform decision making at the national, state, and community levels.

The NIS includes information about all the inpatient hospital stays (regardless of expected payer for the hospital stay) which is derived from billing data submitted by hospitals to state-wide data organisations across the US. This information contains clinical and resources usage information included in a typical discharge abstract. The NIS is a sample drawn from the State Hospitalisation Database (SID), which includes all hospitalisation data currently provided to HCUP. The number of states participating in NIS has increased from 8 in the first year to 48 at present. The NIS is designed to produce

US regional and national estimates of inpatient utilisation, access, cost, quality, and outcomes. From 2004, unweighted, NIS contains data from more than 7 million hospital stays each year. Weighted, it estimates more than 35 million hospitalisations nationally each year making it one of the largest databases worldwide. If the study is to create national estimates, data must be weighted in order to achieve such analyses on the NIS data. Weighting the data enables us to produce nationally representative estimates.

4.2.1 Design

The NIS was redesigned in 2012 to improve national estimates. In order to highlight the design changes, from 2012 data, AHRQ renamed NIS from the "Nationwide Inpatient Sample" to "National Inpatient Sample". The redesign is mainly reflected in three types of changes:

First, the sample design was revised. For the latest NIS design (2012 onwards), a stratified random sample of 20% of discharges from the "universe of discharges" (all discharges from the HCUP hospitals) is used. Strata are defined by census division (US census splits the country into nine geographical divisions), rural/urban location, bed-size, teaching status, and ownership. Weights based on the total numbers of discharges in each stratum are then used to weight estimates to the target population of all US inpatient discharges. Prior to 2012, the NIS used a different source for the "universe of discharges" and weights were based on census region (4 regions) rather than census division. In other words, before 2012, NIS retained all discharges from a sample of hospitals. Since the redesign, NIS is now a sample of discharge records from all HCUP participating hospitals, approximating a 20% stratified sample of discharges from approximately 1000 community hospitals in the US [115]. Hence, for trends analysis using NIS data 2011 and earlier, revised weights

should be used to make estimates comparable to the new design beginning with 2012 data. Moreover, it might be a smaller one-time disruption to temporal trends for rates or means estimated beginning with data year 2012 (could see it in the descriptive table at the end of this chapter). In total, the sampling strategy has changed over time, the new sampling strategy can produce more precise and stable estimates than the previous NIS design by reducing the margin of error for estimates. Second, the definition of discharges and hospitals was changed. The scope of discharge was revised to exclude long-term emergency care hospitals. In addition, NIS now uses the definition of hospitals and discharges based on the state-wide data organisation that contributes to HCUP, rather than the definition used by the American Hospital Association (AHA) Annual survey. Third, confidentiality is enhanced by eliminating state and hospital identifiers and other data elements that are not uniformly available across countries. For example, AHA hospital identifiers, secondary payers, and data elements with country-specific codes are removed. Hence, NIS is a publicly available database that ethical approval is not required. However, HCUP requires all research applicants to finish a data user agreement and mandatory online training. In addition, the elimination of hospital identifiers means that some types of analysis such as hospital volume analysis that relies on a census of discharges from sampled hospitals can no longer be conducted.

4.2.2 Data Elements

The NIS contains clinical and resource-use information, this data is contained in a typical discharge of abstract to protect the privacy of individual patients, physicians and hospitals. The NIS includes clinical and nonclinical data elements for each discharge, including codes on diagnosis, procedures, and external cause of injury prior to October 2015; patient baseline characteristics

such as age, gender, race, admission day (weekday or weekend); hospital characteristics (e.g., ownership, bed size); expected payment source; total charges and length of stay; discharge status (outcomes); severity and comorbidity measures.

4.2.3 Coding Systems

These data elements are stored using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes [116]. NIS includes ICD-9-CM diagnostic and procedure codes for hospitalised patient discharges prior to October 1, 2015. From October 1, 2015, using International Classification of Diseases, Tenth Revision, Clinical Modification/Procedure Coding System (ICD-10-CM/PCS) to report diagnosis and procedure codes. The ICD-9-CM and ICD-10-CM diagnosis and ICD-10-PCS procedure codes provide valuable insights into hospitalisation reasons and what procedures patients receive. In addition, HCUP has developed a Clinical Classification of Software (CCS) scheme which is also based on the ICD-9-CM codes. CCS contains over 14,000 diagnoses and 3,900 procedure codes and enables the analysis like descriptive statistics of diagnoses or procedures more efficiently and accurately. For example, the ICD-9-CM's multitude of codes for any type of in-hospital gastrointestinal bleeding is collapsed into a single CCS diagnosis code. In the study, all eligible data for analysis by identifying the ICD-9-CM, ICD-10-CM, and CSS codes was screened.

4.2.4 File Structures

The file structure of the NIS in this thesis is an annual, calendar year file. There are one hospital-level file and three discharge-level files.

Discharge-level files include Core File, Severity File, Diagnosis and Procedure Groups File. Core File is a single file containing basically used data

elements such as age, gender, payer, discharge status and total charges. Severity File is also a single file including additional data elements for the identification of the severity of conditions for a specific discharge. Diagnosis and Procedure Groups file is a file containing data information on the codes of diagnoses and procedures that were created by AHRQ software tools. Hospital-level file is a single file containing data on hospital characteristics such as bed size of the hospital, location (urban or rural) of the hospital.

4.2.5 Appraisal For Data Source

In this section, the strengths and limitations of the NIS data source for the analyses will be discussed, and then the reliability and relevance of the NIS database to the research questions of this thesis will be evaluated.

4.2.5.1 Strengths and Limitations

As mentioned previously, the NIS database has several strengths: a large scale of the sample, using complex survey design, public accessibility, data availability for multiple years, wide-ranging administrative health records and well-documented resources [117]. The large sample size can greatly increase the statistical power of research exploration. Moreover, national representativeness was a specific objective, achieved by complex sampling methods. The data availability and supporting materials make the NIS an accessible and attractive dataset for research in a well-defined target patient population such as trend analyses [118].

However, the NIS database also has limitations. First, the NIS is inappropriate to be used for doing state-level or physician-level analyses because the sampling design does not provide a representative sample of hospitalisations for states and the available field code has an inconsistent meaning [119]. Second, the database does not contain patient identifiers, it does

not allow the tracking of patients, and therefore it is unavailable to do any long-term longitudinal analyses (such as, estimated time to the occurrence of the outcome of interest, long term outcomes). Meanwhile, as the NIS dataset has no patient identifier, a patient may contribute multiple data entries if the patient was hospitalized more than once within the study period. Multiple admissions may cause potential issues in the results of the analysis. For example, overestimating the proportions for high comorbidity burden groups, affecting the association between comorbidity burden and outcomes, understating the variance of comorbidity measure's prognostic impact, and so on. This issue cannot be examined due to no patient identifier. However, the impact is expected to be relatively small as the data size is enormous and the used modelling method also involves sampling weights for estimation. Third, the NIS lacks data regarding pharmacology and lab results, those data might be helpful in improving the prediction of patient prognosis. Finally, there are challenges to distinguishing postoperative complications from present-on-admission comorbid conditions. However, fortunately, all Elixhauser comorbidities have been contained in the NIS dataset; the codes used to extract in-hospital complication variables were also double-checked with clinicians and have been validated from previous papers.

4.2.5.2 Reliability and Relevance

Based on the above strengths and limitations, how reliable and relevant is the data in the NIS database for addressing the research questions in this thesis?

For analysis of trends over time, the NIS provides rich data on recorded comorbidity among admitted ACS patients over many years, managed and maintained by the AHRQ since 1988. The database additionally provides a trend

weight file that considers weights over the period, adjusting for the changes in sample designs in 2012. Meanwhile, the yearly national estimates of proportions for different categories in comorbidity measures can be obtained by considering the weights. For relating comorbidity at admission to patient outcomes, the NIS includes records of key in-hospital outcomes, invasive procedures and other risk factors, and all the data elements relevant to the questions can be identified by diagnostic and procedure codes and retrieved.

Missing values in the included variables may potentially affect the reliability and relevance of the data for addressing research questions. From initially assessing missing data, there are only a few variables with missing values. Most have a small missing proportion (<2.6%) and only one variable (race) has a more substantial missing proportion (17.6%). It suggests that at least 80% of the data remain as a representative sample for the study population and the analysis results may be still valid to answer study questions. To be cautious, imputation and sensitivity analyses will be also performed for confirming the robustness of analysis results.

4.2.6 Relevant Research Guidelines

Two reporting guidelines for observational research - Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) [120] and Reporting of studies Conducted using Observational Routinely collected Data (RECORD) [121] are relevant to ensuring that the data source and processes and decisions around its use are reported in a full and transparent way. The STROBE guideline was developed by methodologists, researchers and journal editors to recommend investigators for reporting work if observational studies are conducted for a pre-specified research purpose. It is made up of 22 items covering the title, abstract, introduction, methods, results and discussion

sections of articles. 18 of 22 items are common to three designs of observational studies (cross-sectional, case-control, cohort studies). The RECORD statement was created as an extension of STROBE for observational studies using health data routinely collected for administrative and clinical purposes without specific a priori research goals. It consists of a checklist of 13 items further related to the title, abstract, participants, variables, data access and cleaning methods, linkage and the studies limitations. The STROBE and RECORD statements are mainly suitable for publications for research articles or reports, they were useful when publishing the NIS analyses from this thesis.

4.3 PREPARATION OF DATA USED IN THIS THESIS

Before starting the analysis, I underwent the HCUP Data Use Agreement Training which is required before access to the NIS database can be granted. As described above, each analysis in this thesis aimed to explore a specific aspect of ACS patients and each chapter will discuss its own methods in detail, therefore, specifics of data processing for each aim are not listed here. However, It still needs to prepare the data for the subsequent analyses beforehand which includes data linking, data arrangement, data defining, data cleaning, data extracting such as specific conditions, risk factors, procedures, comorbidities and complications following ACS from the NIS database.

4.3.1 Data Linking

As all the data or variables that will be used in this thesis are among the different datasets in the NIS database, so I use data linking to bring together information. Data linking is the process to join different datasets together, it involves horizontal merger (merge) and vertical combination (append), it involves identifying and combining data from corresponding records on each of the

different datasets so that a new, richer dataset can be created. As mentioned in section 4.2.4, according to the file structures in the NIS, our data linking needs a few steps. First, discharge-level files have three files, I need to combine each year data within each file and then generate a variable of the Year in each dataset, then I obtained three files including the core file, severity file and diagnosis file from 2004 to 2014. Then, there is a unique record identifier (KEY prior to 2012, KEY_NIS from 2012) that provides the linkage between the discharge-level files, this indicator assisted by the variable of Year was used to merge these three files. Given the unique identifier changed in 2012, before the merger, I handled the different identifiers into a new variable and adjusted its format ready to use. Next, the hospital-level files were combined into a file including the whole study years. Then, the HCUP hospital identifier was used which is provided to link the datasets between the NIS inpatient Discharge-level files and the Hospital files. Given the hospital identifier was redesigned in 2012 as well (HOSPID prior to the 2012 NIS, HOSP_NIS beginning with the 2012 NIS), a new variable based on this change was created. Both the variable of Year and the hospital identifier were used together to merge datasets, in order to help uniquely identify observations in the master data. Furthermore, since the total charge of hospitalisation provided in the NIS database is the sum billed for by the hospital rather than the actual cost, I used the HCUP cost-to-charge file to convert total costs into actual costs. Finally, the weights changed in 2012 due to the redesign in 2012 NIS (TRENDWT prior 2012, DISCWT beginning in 2012), after previous datasets were merged, it contained these above two variables, so I merged these two variables into a new variable for the weighting estimates in the subsequent analyses.

Finally a rich dataset was obtained that contains all variables needed in the subsequent analyses or not needed. Nevertheless, it still needs further

refining.

4.3.2 Data Manipulation

After the merge of each dataset, I examined the data for their order, completeness and accuracy to identify any potential problems. Meanwhile, data manipulation was conducted which is the process of checking and changing data to make it easier to access or be more organised. In order to make the dataset easier to read and use, I annotated data, generated new indicators, changed some variables' format and organised the variables list. For example, the same variable having different names was respectively stored in two different datasets, I need to combine these two variables into a new variable with annotation after the data merge. Data manipulation can enable people to display information in a more meaningful way, which benefit the subsequent data processing.

4.3.3 Data Cleaning

After manipulating the dataset, preliminary data cleaning was undertaken. First, I checked each variable by summarising their frequency distributions, bar charts or their value tables. Erroneous values for records (lower or upper outliers that were beyond the acceptable range) were removed. For instance, the records in the age variable which are older than 110 years or younger than 18 years were removed (0.009%).

Then, I started to identify all eligible patients with a primary diagnosis of ACS from 2004 to 2014 by using ICD-9-CM diagnosis codes 410.xx (AMI) and 411.1 (UA). Next, all baseline patient characteristics for each discharge were extracted including age, gender, race, admission day (weekday or weekend), median household income for patient’s ZIP code; weighting variables; mortality and so on. In addition, the NIS database includes up to 30 diagnoses and 15

procedure codes, which were used to identify the conditions, procedures, comorbidities and complications of interest for this thesis, these 45 variables were kept. Other variables which are used in the subsequent analyses will be identified or generated in the corresponding chapters. In total, the ICD-9-CM codes that were used in this thesis were collected in three stages: first, from a systematic search of EMBASE and MEDLINE for papers that had studied ACS using read codes. Second, by searching clinicalcodes.org for studies that had reported on AMI using read codes. The results collected from these two stages were then checked through CCS codes for ICD-9-CM for whether they referred to events corresponding to ACS or not. Finally, using a consensus strategy, read codes identified from the stages above were double-checked by clinicians and interventional cardiologists in the wider research group. The finally relevant ICD-9-CM codes were extracted into an Excel spreadsheet and used to extract the required data and identify the variables of interest for the planned studies and can be found in the next chapter (**Appendix Table 5.1a)**.

Finally, a dataset containing all ACS patient discharges from 2004 to 2014 was created. A basic descriptive analysis was performed to assess the structure of the dataset, missing values and the distribution of the data. For continuous variables, the mean, standard deviation, median, maximum, minimum and missing percentages were explored; for categorical variables, the frequency and percentages (based on the non-missing sample size), percentage of missing values were checked. All the statistics are weighted estimates using sampling weights. Any extreme outliers (such as age) would be queried for clinical validity and discarded from analysis if unfeasible. During this process, a preliminary selection of baseline patient variables and clinically relevant comorbidities that are contained in the NIS dataset was conducted based on their clinical importance which were recognised by clinicians and double

checked with previous related studies and rule of thumb, an agreement was reached with clinicians that some baseline variables were not included in the subsequent analyses according to the research aims, referring to previous studies and the rule of thumb, such as type of hospital, bed size of hospital, elective versus non-elective admission and so on.

The summary table of the basic descriptive analysis above is listed in **Table 4.1** including the percentages of missing observations.

Table 4.1: Secular trends of baseline characteristics between 2004 and 2014 in ACS patients (7,201,900).

Variable	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Missing
Patients' demographics												
No. of weighted discharges with ACS diagnosis	740,955	695,515	703,225	648,254	656,054	643,732	612,107	615,518	633,110	624,264	629,165	None
No. of weighted discharges with STEMI diagnosis	288,901 39%	262,322 38%	262,641 37%	224,753 35%	221,010 34%	203,699 32%	191,413 31%	186,241 30%	184,550 29%	179,470 29%	175,810 28%	None
Median (IQR) age, y	68 (57-79)	68 (56-80)	67 (56-79)	67 (56-79)	68 (56-79)	67 (56-79)	67 (56-79)	67 (57-79)	67 (57-78)	67 (57-78)	67 (57-78)	648 (0.009%)
Female, %	41.8%	41.5%	40.6%	41.0%	40.9%	40.1%	40.0%	39.8%	38.4%	38.8%	38.5%	1,035 (0.014%)
Race, %												
White	55.9%	57.3%	57.0%	55.9%	61.7%	63.3%	65.6%	66.9%	71.0%	70.7%	71.0%	1,255,683 (17.4%)
black	7.0%	5.5%	6.7%	7.5%	7.4%	7.8%	9.9%	9.7%	10.1%	10.1%	10.2%	
Hispanic	5.2%	5.5%	5.8%	5.6%	5.3%	6.1%	6.4%	7.4%	7.2%	7.6%	7.4%	
Asian/Pacific islander	1.5%	1.2%	1.4%	1.8%	1.9%	1.8%	2.0%	2.0%	2.1%	2.3%	2.3%	
Native American	0.2%	0.2%	0.4%	0.5%	0.7%	0.5%	0.4%	0.6%	0.5%	0.5%	0.5%	
other	2.0%	2.3%	2.0%	2.3%	2.9%	3.6%	2.4%	2.9%	3.2%	2.8%	3.0%	
Missing Race	28.1%	27.9%	26.7%	26.4%	20.1%	16.9%	12.8%	10.6%	5.9%	6.1%	5.5%	
Admission/weekend, %	25.0%	25.1%	24.9%	25.5%	26.3%	25.9%	26.4%	26.2%	25.9%	26.5%	26.3%	None
Median zip code income national quartile, %												
Frist	28.3%	28.4%	27.1%	28.6%	28.3%	29.0%	29.3%	29.2%	31.5%	30.0%	29.6%	172,846 (2.4%)
Second	28.1%	26.5%	27.1%	26.1%	29.2%	28.0%	27.1%	25.7%	26.1%	27.7%	29.3%	
Third	22.4%	24.4%	24.3%	23.6%	22.6%	23.6%	23.8%	25.4%	23.0%	23.4%	22.7%	
Fourth	21.2%	20.7%	21.4%	21.7%	20.0%	19.4%	20.0%	20.0%	19.5%	19.0%	18.4%	
Clinical outcomes, %												
Mortality	6.6%	6.3%	5.8%	5.7%	5.7%	5.3%	5.1%	5.1%	5.0%	4.8%	4.8%	2,881 (0.04%)

Chapter 5 -
Prognostic Impacts of Charlson Comorbidity Index on ACS outcomes

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Impact of Charlson Comorbidity Index Score on management and outcomes after Acute Coronary Syndrome

5.1 INTRODUCTION

In line with the first aspect as set out in Section 1.1 in this thesis, this chapter mainly investigates Objective two by exploring the temporal trends in comorbidity burden and impact on prognosis in patients with ACS using CCI. The findings from this chapter have been published in The American Journal of Cardiology.

As stated above, CVDs cause approximately one-third of all deaths in the world and remain the leading cause of death in the US [46]. A significant proportion of patients with CVDs have concurrent comorbid conditions [77, 122]. Moreover, this proportion is increasing every year, especially for ACS patients with moderate to severe comorbidity burden [54]. It is well established that patients with a significant comorbidity burden are at increased risk of adverse outcomes and are challenging to treat [56]. At an individual level, increasing comorbidity burden in patients with ACS is associated with an increased risk of mortality and future CV events [57, 58], which brings challenges to treatment strategies, rehabilitation potential and prognosis; at a population level, increasing comorbidity burden also has brought a heavy economic burden to the medical system such as the increase in the length of hospital stay and hospital cost [55]. In future, the frail elderly with multiple comorbidities are predicted to represent a greater proportion of the ACS population [123]. Therefore, it has become important to study the prognostic impact of the comorbid burden on ACS outcomes and treatment strategies to guide clinical management.

It was mentioned earlier that the comorbidities rarely occur in isolation and should be considered in totality, considering both CV and non-CV conditions [88, 89]. CCI is a method to measure the overall comorbidity burden

and its scoring system was developed as a prognostic indicator for patients with multiple medical conditions. CCI has been proven to predict mortality and morbidity and the risk of repeated hospitalisations of different populations [70, 77, 78].

From the results from the review in Chapter 3, it is found that previous studies evaluating the impact of CCI on ACS outcomes were generally limited to old datasets with small sample sizes [96], single centre studies [60], specific cohorts of patients, such as first-time hospitalisation for AMI [54], STEMI [124], or focused only on the incidence of ACS instead of outcomes [125]. In addition, some of the previous studies [126, 127] used the CCI method as a confounder rather than reporting its prognostic impact estimates, which meant its focus was not on the impact of CCI comorbidity burden on ACS prognosis. Therefore, from a national perspective, there is still limited data regarding the epidemiological changes in demographics, risk profile, CCI-defined CV and non-CV comorbidities of ACS patients over the past decade; also lack of data on the impact of CCI measure on the management and outcome of ACS patients.

As such, it is necessary to update and expand the research results in this field. The research in this chapter will use the US national database to study the temporal trend in baseline characteristics, comorbidity burden (measured by the CCI score), amongst patients with ACS in the last 11 years, as well as evaluate the impact of CCI scores on the use of invasive management and subsequent clinical outcomes of ACS patients.

5.2 SPECIFIC OBJECTIVES

The specific objectives of this chapter are as follows:

I. To analyse the temporal trends in demographic characteristics, Charlson comorbidities, specific conditions, procedures and complications in

patients with ACS.

II. To investigate the trend in above variables stratified according to the CCI.

III. Fitting models to study the association of comorbidity burden with in-hospital mortality, MACCE, major bleeding, and use of treatments in patients with ACS.

IV. To visualize the results and trends.

5.3 METHODS

5.3.1 Data Processing

Full details of the database that was used (NIS dataset) have already been described in Chapter 4. However, each chapter has a specific goal and requires a targeted processing of the original dataset. A brief summary of this data processing is provided here.

An original dataset was obtained in the data source chapter, however, some variables for this chapter are still needed which are CCI comorbidities not contained in the NIS dataset, treatment variables used as secondary outcomes in the subsequent analysis, clinical complications variables treated as primary outcomes (except for mortality). The NIS database includes up to 30 diagnoses and 15 procedure codes, which are used to identify the specific conditions, procedure and outcomes variables. Thus, all the above variables were generated by using ICD-9-CM codes which were identified from previous papers and doubled checked with clinicians. A list of ICD-9-CM codes used to extract those variables is provided in **Appendix Table 5.1a**. Next, the 17 CCI comorbidities variables were processed into a single CCI score variable. Each comorbidity defined by Charlson et al was assigned a weighted score (**Appendix Table 5.1b**) according to the association of this comorbidity with 1-year all-cause mortality in the original cohort [72]. The CCI score variable was created based on this

weight system by summing all individual weights into a total score. Then, the CCI score variable was stratified according to the severity of comorbidity burden into 4 groups: “0” (no comorbidity), “1” (mild comorbid burden), “2” (moderate comorbid burden), “≥3” (severe comorbid burden). Finally, based on the original dataset, a new dataset was obtained that includes extra variables such as procedures, outcomes, CCI individual comorbidities, CCI scores in continuous type and in categorical type.

5.3.2 Study Design and Outcomes

The study period was from January 2004 to December 2014. All adults (≥18 years) with the principal diagnosis of ACS were eligible for inclusion. Baseline patient characteristics for each discharge includes age, gender, race, admission day (weekday or weekend), median income, 17 comorbidities using Deyo modification of the CCI [74] and other clinically relevant comorbidities (smoking, atrial fibrillation, long-term use of anticoagulants, prior PCI and prior CABG). Treatment or procedure variables include PCI, CA, CABG, intra-aortic balloon pump (IABP) and infusion of the thrombolytic agent.

The primary outcomes of interest were in-hospital mortality, MACCE and major bleeding. Their definition was described in Section 2.1.6 in Chapter 2. Secondary outcomes included the receipt of invasive management (PCI or CA), length of stay and total hospitalisation charges.

5.3.3 Statistical Analysis

The survey estimation commands were used for all analyses considering the complex survey design of the NIS database in compliance with AHRQ recommendations. Since the records from NIS were sampled by hospitals instead of individuals and represent collections from hospital clusters across the US community hospitals, analyses were conducted with a consideration of

this multistage, probability sampling. Because the design of the hierarchical structure of NIS dataset means that different records may be drawn with different probabilities, each hospital discharge is linked to a sampling weight that was used in all analyses to calculate national estimates.

Apart from the basic analysis for demographic variables in Chapter 3 of data source, temporally descriptive analyses based on CCI comorbidities, CCI scores, other relevantly specific conditions, treatment variables and clinical outcomes were performed. Then, descriptive statistics of all the baseline variables stratified by CCI categories were analysed. Categorical variables are expressed as percentages or absolute numbers whereas continuous variables are presented as median values with corresponding interquartile range (IQR) due to their skewed distribution.

As mentioned in the data source chapter, the NIS dataset has missing values in the baseline variables. After the basically descriptive analysis and before fitting the model, the missing data was imputed. First, missing data was assumed to be missing at random since the missing indicator of the variable “race” which was the variable with the largest proportion of missing data was associated with socio-economic "household income" variable which was also included in imputation models. Next, multiple imputations by chained equations (MICE) [128, 129] was conducted to impute missing data in age, sex, race, home income and mortality variables. The number of imputation datasets equal to the highest proportion of missing data for any particular variable according to the rule of thumb for the number of imputation datasets proposed by White et al. [129] (this rule suggested the number of imputation datasets should be at least equal to the percentage of incomplete cases). Model parameters were estimated within imputation datasets and combined using Rubin’s Rules [130]. All outcomes and other covariates including age, gender,

home income, CCI score variable, year of hospitalisation and so on were included in the imputation model to ensure congeniality with the analysis model [131].

To evaluate the association between CCI and in-hospital outcomes and the receipt of invasive management, multivariable logistic models using maximum likelihood estimation were fitted. The following potential confounders selected in Section 5.3.2 were added into the multivariable analysis: age, gender, race, household income, day of admission, smoking status, diagnosis of atrial fibrillation, long-term use of anticoagulants, prior PCI, prior CABG, use of PCI, CA or CABG during admission, use of IABP, infusion of thrombolytic agent and year of hospitalisation. Variables that form part of the CCI score were not adjusted for to avoid collinearity (such as previous MI and dementia). The "CCI=0" group was used as the reference category for all analyses. The prognostic impact of each individual CCI comorbidities on the use of treatments and ACS outcomes was investigated. Finally, a sensitivity analysis was performed using CCI score as a continuous variable to assess the impact of per unit score of CCI on in-hospital outcomes. Statistical analyses were performed using STATA version 14.0. ORs and their corresponding 95% CIs were used to report the results of models.

5.4 RESULTS

From 2004 to 2014, a total of 7,201,900 weighted records≥18 years of age with a principal diagnosis with ACS were included in the analysis, providing sufficient statistical power. The process of excluding data is listed in **Appendix Figure 5.1**. In total, there is about 19.4% of missing data mainly found in race (17.4%), age (0.009%), gender (0.014%), household income (0.014%) and death (0.04%) variables.

Descriptive statistics of baseline characteristics, treatments, outcomes, and comorbidities before multiple imputations are listed in **Table 5.1**. The median age of ACS patients was 67 (56-79) years old and changed little over the study period while the proportion of women decreased during the 10 years from 41.8% to 38.5% (2004-2014) (**Table 5.1**). The percentage of patients with STEMI decreased from 39% in 2004 to 28% in 2014. Among 17 Charlson comorbidities, the prevalence of several CV risk factors (previous MI, 7.9%-12.9%, peripheral vascular disease (PCV) 1.2%-1.7%, previous CVD 1.8%-9.4%, and diabetes 25.6%-31.8%) increased over the study years. The prevalence of non-CV comorbidities such as metastatic disease, liver disease and chronic pulmonary disease (CPOD) also increased over the same period. (**Table 5.1**).

Table 5.2 demonstrates patient demographics stratified by CCI across all years. Patients with a higher comorbid burden (CCI≥2) were older compared to those with a lower burden or no burden. Female patients were less prevalent than male patients in all the groups studied, however, females were more common in the severe comorbid burden cohort (45.7% in CCI≥3 vs. 33.9% in CCI=0). The percentage of patients without any comorbidities (CCI=0) declined from 37.3% in 2004 to 30.2% in 2014, whilst the percentage of patients with the severe comorbid burden (CCI≥3) increased from 10.8% to 18.1%. **(Figure 5.1**) 34.2% of patients had no Charlson comorbidities while the percentage of patients with CCI≥3 was 13.8%.

Table 5.1: Secular trends of baseline characteristics between 2004 and 2014 in ACS patients (7,201,900).

	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Missing
Charlson Comorbidities, %												
Previous Myocardial infarction	7.9%	7.9%	8.6%	9.1%	9.3%	10.3%	11.0%	11.7%	12.0%	12.4%	12.9%	None
Congestive heart failure	30.3%	30.1%	28.5%	28.7%	28.3%	28.7%	29.1%	30.2%	29.9%	30.5%	31.0%	None
Peripheral vascular disease	1.2%	1.2%	1.3%	1.3%	1.5%	1.7%	1.6%	1.6%	1.6%	1.6%	1.7%	None
Previous Cerebrovascular disease	1.8%	1.7%	1.7%	2.5%	6.0%	7.2%	7.7%	8.6%	8.8%	8.9%	9.4%	None
Dementia	0.7%	0.8%	0.8%	0.7%	0.7%	0.7%	0.6%	0.7%	0.6%	0.5%	0.5%	None
Chronic pulmonary disease	19.4%	20.5%	20.2%	20.5%	19.4%	20.1%	20.0%	21.0%	21.0%	21.1%	21.4%	None
Rheumatologic disease	1.6%	1.7%	1.7%	1.8%	1.9%	1.9%	2.0%	2.1%	2.3%	2.3%	2.3%	None
Peptic ulcer	1.2%	1.1%	1.0%	1.0%	1.0%	1.1%	1.0%	1.0%	1.0%	0.9%	0.9%	None
Mild liver disease	0.4%	0.4%	0.4%	0.4%	0.3%	0.4%	0.4%	0.5%	0.5%	0.5%	0.6%	None
Diabetes	25.6%	25.5%	26.1%	27.1%	27.4%	28.5%	29.1%	30.2%	31.1%	31.4%	31.8%	None
Diabetes with chronic complications	3.7%	3.7%	3.6%	4.2%	4.2%	4.6%	4.8%	5.6%	5.6%	5.8%	6.1%	None
Hemiplegia or paraplegia	0.4%	0.3%	0.3%	0.4%	0.5%	0.5%	0.5%	0.4%	0.4%	0.4%	0.5%	None
Renal Disease	1.4%	1.1%	0.4%	0.5%	0.8%	0.9%	1.2%	1.3%	1.2%	1.3%	1.4%	None
Any malignancy inc. leukaemia and lymphoma	2.4%	2.6%	2.4%	2.7%	2.8%	2.8%	2.7%	2.8%	2.8%	2.9%	3.0%	None

	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Missing
Moderate or severe liver disease	0.1%	0.1%	0.1%	0.2%	0.2%	0.2%	0.2%	0.2%	0.3%	0.2%	0.3%	None
Metastatic solid tumour	0.7%	0.8 %	0.8%	0.9%	0.9%	0.9%	0.8%	0.9%	0.8%	0.8%	0.9%	None
AIDS	0.1%	0.1%	0.1%	0.1%	0.1%	0.2%	0.2%	0.2%	0.1%	0.1%	0.1%	None
Charlson Comorbidity Index Score, %												
0 (CCI=0)	37.3%	37.0%	37.4%	36.2%	35.0%	34.2%	33.5%	32.1%	31.6%	31.0%	30.2%	None
1 (CCI=1)	33.1%	33.2%	33.6%	33.1%	33.1%	32.1%	32.0%	31.1%	31.4%	31.3%	31.1%	None
2 (CCI=2)	18.7%	18.9%	18.7%	19.0%	19.3%	19.4%	19.7%	19.9%	20.3%	20.5%	20.6%	None
3 (CCI≥3)	10.8%	10.9%	10.4%	11.7%	12.7%	14.2%	14.8%	16.8%	16.8%	17.2%	18.1%	None
Other conditions, %												
Smoking	24.7%	27.0%	28.9%	30.3%	31.7%	34.7%	36.0%	37.6%	39.6%	41.1%	43.8%	None
Atrial Fibrillation	15.9%	16.3%	16.3%	16.2%	15.4%	16.0%	16.2%	17.5%	17.5%	17.7%	18.3%	None
Long-term AC use	1.4%	1.7%	1.9%	2.3%	2.4%	3.1%	3.4%	3.9%	3.9%	3.9%	4.4%	None
Previous PCI	6.5%	7.2%	8.4%	9.4%	10.2%	11.6%	12.5%	14.3%	14.8%	15.4%	16.2%	None
Previous CABG	6.7%	6.6%	6.7%	6.6%	7.0%	7.6%	7.7%	8.6%	8.3%	8.3%	8.5%	None
Treatments/procedural characteristics, %												
PCI	32.9%	35.4%	38.6%	38.0%	40.0%	41.9%	42.2%	43.2%	45.2%	46.2%	46.7%	None
Coronary Angiography	53.3%	56.4%	58.2%	59.0%	60.3%	63.4%	64.2%	64.3%	67.6%	68.6%	69.3%	None
Infusion of thrombolytic agent	1.7%	1.7%	1.6%	1.3%	1.4%	1.2%	1.0%	1.2%	1.1%	1.1%	1.1%	None
CABG	8.8%	8.4%	9.0%	8.4%	8.2%	8.7%	7.9%	7.8%	8.2%	8.4%	8.4%	None
IABP use	4.1%	4.4%	4.6%	4.6%	5.0%	5.0%	4.7%	4.7%	4.6%	4.4%	4.2%	None

AC: Anticoagulants; ACS: acute coronary syndrome; IQR: interquartile range; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; CCI: Charlson Comorbidity index; IABP: intra-aortic balloon pump.

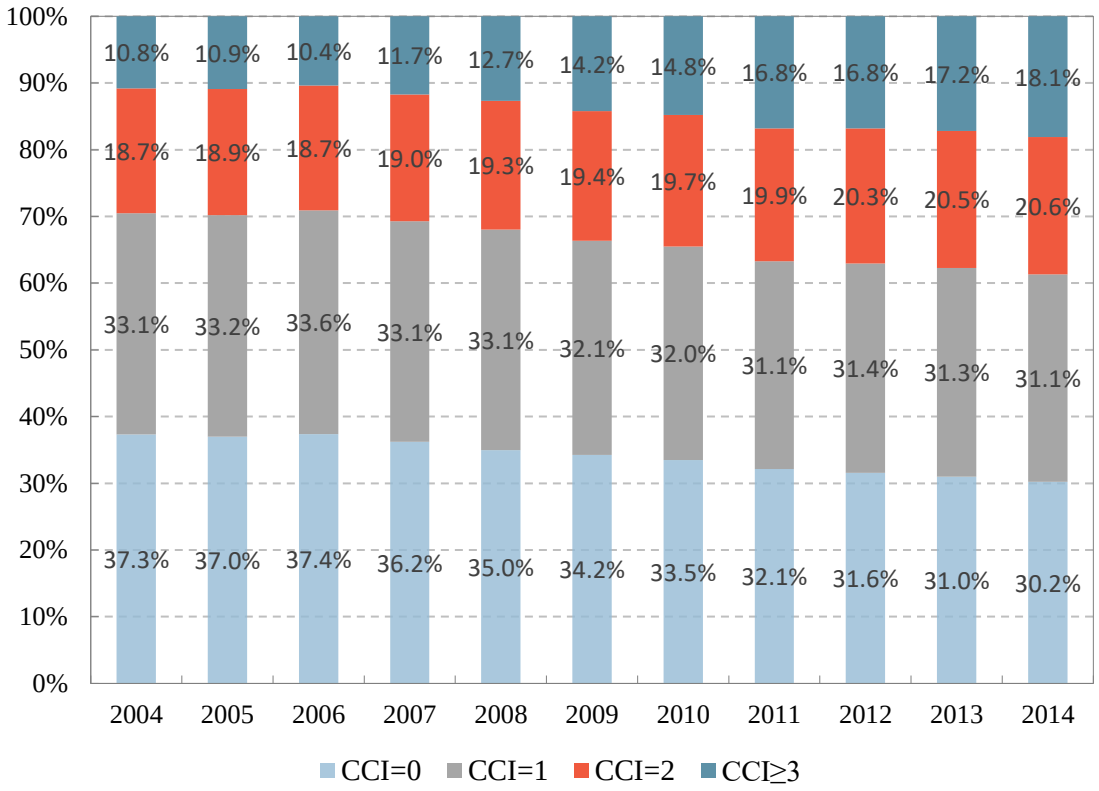
Table 5.2: Patient demographics stratified by categorised Charlson Comorbidity Index Score (CCI).

	Charlson Comorbidity Index Score (CCI)			
	CCI =0	**CCI =1**	**CCI =2**	**CCI ≥3**
Patient demographics				
No. of weighted discharges with ACS diagnosis	2466301 (34.2%)	2328309 (32.3%)	1406418 (19.5%)	1000872 (13.9%)
Median (IQR) age, y	62(52, 74)	68(57, 80)	72(61, 82)	72(63, 81)
Female, %	33.9%	41.8%	44.6%	45.7%
Race, %				
White	63.5%	62.1%	63.0%	63.7%
black	6.8%	8.3%	9.1%	10.4%
Hispanic	5.5%	6.5%	6.6%	7.1%
Asian/Pacific islander	1.7%	1.8%	1.8%	2.1%
Native American	0.4%	0.4%	0.5%	0.5%
other	2.7%	2.7%	2.5%	2.4%
Missing Race	19.1%	17.9%	16.3%	13.4%
Admission/weekend,%	26.0%	25.7%	25.7%	25.7%
Median zip code income national quartile, %				
Frist	26.2%	30.0%	31.4%	31.1%
Second	27.0%	27.7%	27.7%	27.2%
Third	24.4%	23.2%	22.8%	23.2%
Fourth	22.5%	19.4%	18.1%	18.5%
Resource utilisation. (Median/IQR)				
Median (IQR) length of stay (LOS), d	3(2, 4)	3(2, 6)	4(2, 7)	5(3, 8)
Median (IQR) adjusted cost of hospitalisation, $	$17675 ($14556,$22 123)	$19660 ($14271,$23 844)	$20611 ($13897,$24 930)	$21139 ($13910,$2538 9)
Charlson Comorbidity, %				
Previous Myocardial infarction	N/A	9.1%	17.3%	28.0%
Congestive heart failure	N/A	26.7%	55.8%	72.2%
Peripheral vascular disease	N/A	1.2%	2.5%	4.4%
Previous Cerebrovascular disease	N/A	3.7%	9.6%	18.9%
Dementia	N/A	0.4%	1.2%	2.2%
Chronic pulmonary disease	N/A	19.0%	37.8%	49.6%
Rheumatologic disease	N/A	1.9%	3.4%	4.9%

	Charlson Comorbidity Index Score (CCI)			
	CCI =0	**CCI =1**	**CCI =2**	**CCI ≥3**
Peptic ulcer	N/A	0.8%	1.8%	2.9%
Mild liver disease	N/A	0.2%	0.6%	1.9%
Diabetes	N/A	37.0%	49.2%	49.3%
Diabetes with chronic complications	N/A	N/A	6.1%	25.0%
Hemiplegia or paraplegia	N/A	N/A	0.5%	2.3%
Renal Disease	N/A	N/A	0.7%	6.5%
Any malignancy including leukaemia and lymphoma	N/A	N/A	2.9%	15.4%
Moderate or severe liver disease	N/A	N/A	N/A	1.3%
Metastatic solid tumour	N/A	N/A	N/A	6.0%
AIDS	N/A	N/A	N/A	1.0%
Other specific conditions, %				
Smoking	38.0%	33.0%	30.5%	30.5%
Atrial Fibrillation	10.4%	17.2%	21.9%	23.4%
Long-term use of anticoagulants	1.8%	2.8%	3.8%	4.5%
Previous PCI	7.3%	12.0%	14.1%	15.6%
Previous CABG	4.1%	7.3%	10.3%	12.3%
Treatments/procedural characteristics, %				
PCI	53.5%	40.7%	30.3%	24.0%
Coronary Angiography	72.0%	62.5%	54.2%	47.0%
Infusion of thrombolytic agent	1.8%	1.3%	1.0%	0.8%
CABG	7.2%	9.2%	9.4%	7.8%
IABP use	3.8%	5.1%	5.2%	4.1%

ACS: acute coronary syndrome; IQR: interquartile range; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; IABP: intra-aortic balloon pump.

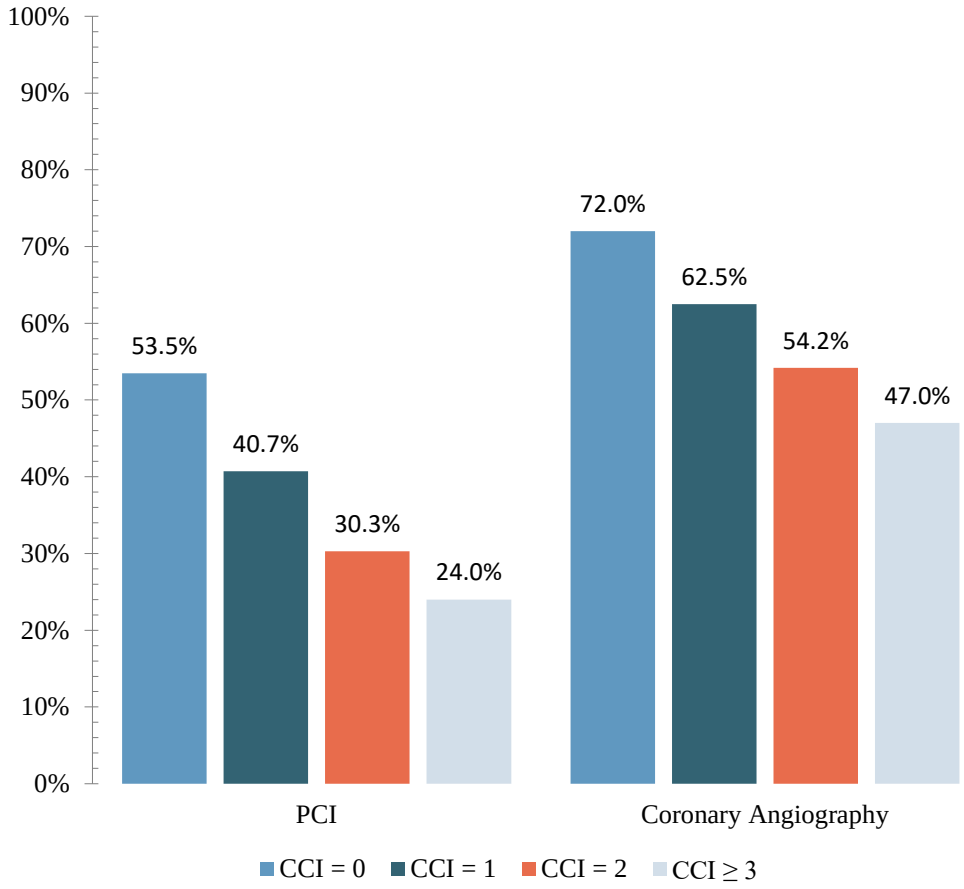
Figure 5.1: Distribution of the CCI groups across the study years (2004-2014).



5.4.1 Management Strategy

The rates of PCI and CA increased over years (32.9% in 2004 to 46.7% in 2014; 53.3% in 2004 to 69.3% in 2014, respectively). **(Figure 5.2)** However, rates of utilisation of CABG remained stable during this decade. **(Table 5.1)** Comorbidity burden negatively correlated with the rate of utilisation of PCI and CA (PCI: 53.5% in CCI=0 to 24.0% in CCI≥3; CA: 72.0% in CCI=0 to 47.0% in CCI≥3) **(Table 5.2).** In comparison to patients with no comorbidities (CCI=0), patients in CCI=2 were 51% less likely in the odds of receiving a PCI whereas those with CCI≥3 were 65% less likely (OR 0.49, 95%CI 0.47-0.50 in CCI=2 and OR 0.35, 95%CI 0.34-0.36 in CCI≥3). A similar pattern was found in the receipt of CA. **(Table 5.3)**.

Figure 5.2: Rates of PCI and CA according to CCI groups between 2004 and 2014.



5.4.2 Clinical Outcome

The rates of MACCE, mortality and major bleeding decreased over the included years (2004-2014), while the prevalence of cardiac complications increased negligibly over time. The rates of acute ischemic stroke and vascular complications did not change. **(Table 5.4)** The rates for MACCE, mortality, acute ischemic stroke and major bleeding increased with increasing comorbid burden (MACCE: 5.4% in CCI=0 to 11.4% in CCI≥3; mortality: 3.3% in CCI=0 to 8.1% in CCI≥3; acute ischemic stroke: 0.9% in CCI=0 to 3.0% in CCI≥3; major bleeding: 3.9% in CCI=0 to 6.1% in CCI≥3). **(Figure 5.3, Table 5.5)**

The results of multivariable regression demonstrated increased comorbid burden was independently associated with increased odds of MACCE, mortality

and major bleeding **(Table 5.3)**. For example, compared with the reference category (CCI=0), CCI=1 was significantly associated with a 21% increase in the odds of MACCE (OR: 1.21, 95% CI: 1.19-1.24), a CCI score of 2 had a 32% increase (OR: 1.32, 95% CI: 1.29-1.35), CCI≥3 had a 1.65-fold (OR: 1.65, 95% CI: 1.61-1.69). Similarly, CCI=1 in in-hospital mortality had 1.31 times increase in the odds (OR 1.31, 9%CI 1.29-1.34); a CCI score of 2 was associated with an almost 1.5 times increase (OR 1.46, 95% 1.42-1.50); the patients with CCI≥3 have an 80% increase in the odds of mortality (OR 1.80, 95% 1.75-1.86). Patients with CCI scores of 1, 2, ≥3 increased in the odds of in-hospital complications (acute ischemic stroke, major bleeding) compared to those patients with a CCI score of 0. The vastest impact was found in acute ischemic stroke with a score of ≥3 (OR: 2.49, 95% CI: 2.37-2.61).

The results of the sensitivity analysis by keeping CCI as a continuous variable are presented in **Appendix Table 5.2** with similar findings to the main analysis. Each unit increase in the CCI score was associated with increased odds of all outcomes. For instance, per unit increase in the CCI score was associated with a 1.12-fold increase in the odds of MACCE (OR 1.12, 95% CI 1.11-1.13). The prognostic impact of each individual Charlson comorbidity using multivariable models on clinical outcomes was presented in **Appendix Table 5.3**.

Table 5.3: Association between categorised Deyo Charlson index scores and recipient of treatments, in-hospital clinical outcomes with ACS diagnosis (adjusted odds ratio, 95% confidence intervals † §).

	Charlson Comorbidity Index Score (CCI)		
Outcomes*	**CCI =1**	**CCI =2**	**CCI ≥3**
PCI†	0.70 (0.69, 0.71)	0.49 (0.47, 0.50)	0.35 (0.34, 0.36)
CA†	0.79 (0.78, 0.80)	0.62 (0.61, 0.63)	0.45 (0.44, 0.46)
MACCE§	1.21 (1.19, 1.24)	1.32 (1.29, 1.35)	1.65 (1.61, 1.69)
Mortality§	1.31 (1.29, 1.34)	1.46 (1.42, 1.50)	1.80 (1.75, 1.86)
Acute ischemic stroke§	1.28 (1.23, 1.33)	1.54 (1.47, 1.61)	2.49 (2.37, 2.61)
Major Bleeding§	1.17 (1.14, 1.20)	1.36 (1.32, 1.40)	1.69 (1.64, 1.75)

*Reference is CCI=0; ACS: acute coronary syndrome; PCI: percutaneous coronary intervention; CA: coronary angiography; MACCE: major acute cardiovascular and cerebrovascular events: composite of death, cardiac complications, stroke, and vascular complications; PCI: percutaneous coronary intervention; CA: coronary angiography.

† Adjustment for age, gender, ethnicity, day of admission (weekday/weekend), median income, type of ACS, If the patient smokes, diagnosis of atrial fibrillation, long-term use of anticoagulants, previous procedure of percutaneous coronary intervention, previous procedure of coronary artery bypass graft, use of intra-aortic balloon pump, infusion of thrombolytic agent and year of hospitalisation.

§ Adjustment for age, gender, ethnicity, day of admission (weekday/weekend), median income, type of ACS, If the patient smokes, diagnosis of atrial fibrillation, long-term use of anticoagulants, previous procedure of percutaneous coronary intervention, previous procedure of coronary artery bypass graft, use of percutaneous coronary intervention, coronary angiography, coronary artery bypass graft, use of intra-aortic balloon pump, infusion of thrombolytic agent and year of hospitalisation.

Table 5.4: Secular trends of clinical outcomes/complications between 2004 and 2014 in ACS patients (7,201,900).

Variable	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Missing
Clinical outcomes/ complications, %												
MACCE	8.7%	8.6%	8.2%	8.1%	8.4%	8.0%	7.5%	7.3%	7.2%	7.2%	7.2%	None
Mortality	6.6%	6.3%	5.8%	5.7%	5.7%	5.3%	5.1%	5.1%	5.0%	4.8%	4.8%	2881 (0.04%)
Acute ischemic stroke	1.6%	1.6%	1.7%	1.6%	1.8%	1.6%	1.6%	1.5%	1.4%	1.4%	1.6%	None
Major Bleeding	5.7%	5.3%	5.3%	5.4%	5.4%	5.1%	4.5%	4.2%	4.0%	3.8%	3.6%	None

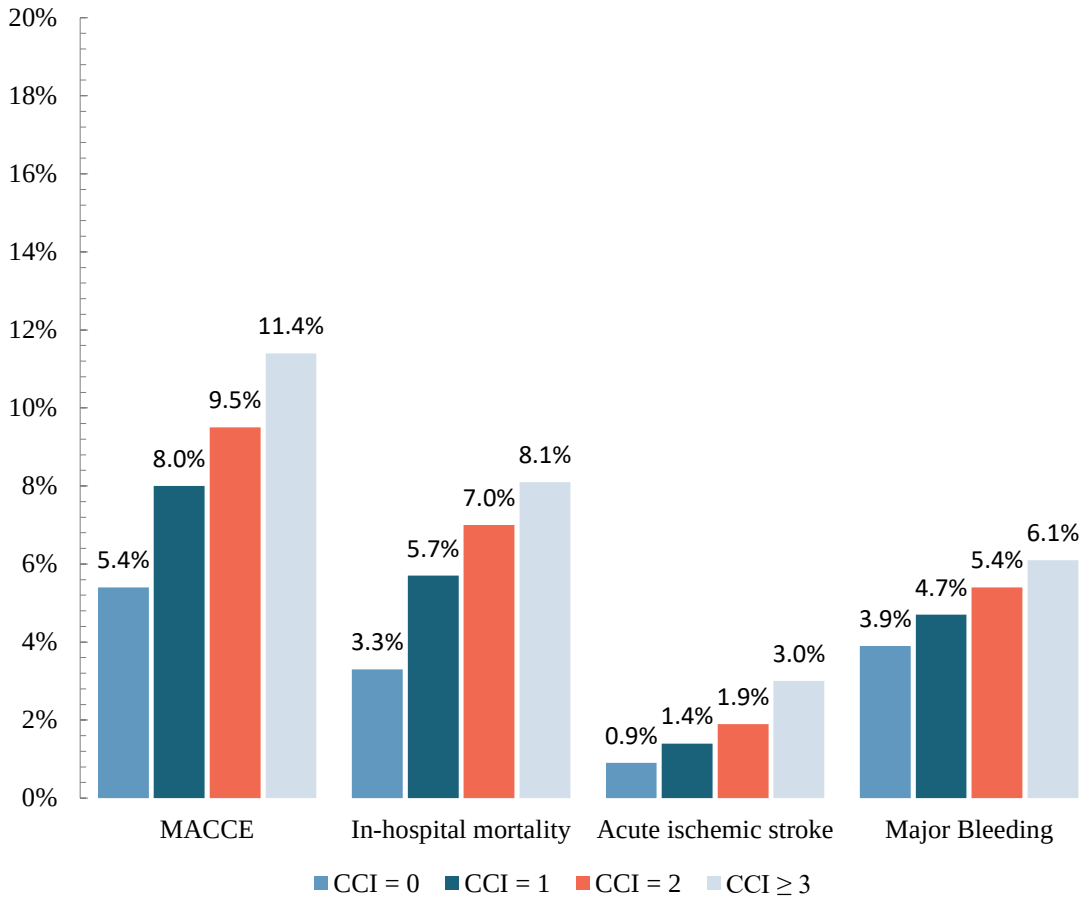
ACS: acute coronary syndrome; MACCE: major acute cardiovascular and cerebrovascular events: composite of death, cardiac complications, stroke, and vascular complications.

Table 5.5: In-hospital clinical outcomes by categorised Charlson Comorbidity Index Score (CCI).

	Charlson Comorbidity Index (CCI)			
Outcomes	**CCI =0**	**CCI =1**	**CCI =2**	**CCI ≥3**
MACCE	5.4%	8.0%	9.5%	11.4%
Mortality	3.3%	5.7%	7.0%	8.1%
Acute ischemic stroke	0.9%	1.4%	1.9%	3.0%
Major Bleeding	3.9%	4.7%	5.4%	6.1%

MACCE: major acute cardiovascular and cerebrovascular events: composite of death, cardiac complications, stroke, and vascular complications.

Figure 5.3: Rates of MACCE, mortality, acute ischemic stroke and major bleeding according to CCI groups between 2004 and 2014.



5.4.3 Length of Stay and Cost

Patients with a CCI score of 0 and 1 had a similar median length of stay (3 days), which was up to 4 days for CCI=2 and 5 days for CCI≥3. (**Table 5.2**) A similar trend was also found in the association of hospital costs with increasing comorbid burden: a median cost of hospitalisation increased from $17,675 in CCI=0 to $21,139 in CCI≥3.

5.5 DISCUSSION

It presents a large study analysing the temporal trends in comorbidity burden (characterized by the CCI) and their impact on prognosis in patients with ACS. It reports an almost doubling of the proportion of ACS patients with

the severe comorbidity burden as defined by CCI, with the prevalence increasing from 10.8% to 18.1% over a period of ten years (2004-2014). This was in the absence of any obvious change in the age distribution and a slight reduction in the proportion of female patients. It was observed that increasing comorbidity burden was associated with an increased risk of in-hospital mortality, MACCE, acute ischemic stroke and major bleeding even after adjustment whilst ACS patients with a heavier comorbidity burden were less likely to receive invasive treatments in form of CA or PCI. Finally, it reported that a severe comorbid burden had an increase in the cost of hospitalisation and length of stay.

The analysis reveals that patients presenting with ACS are increasingly comorbid including CV (history of previous MI, atrial fibrillation including long-term use of anticoagulation, diabetes and its chronic complications, previous CVD) and non-CV (cancer, rheumatological, hepatic and CPOD) diseases. Previous studies have shown that the prevalence of CV-related comorbidities such as diabetes, hypertension, heart failure and atrial fibrillation in acute MI patients had increased between 1990 and 2007 [122, 132]. However, these studies were either small in sample size or community-based studies restricted to a particular geographic area. In addition, it was noted that ACS patients with a severe comorbid burden (CCI≥3) were older (median age was 10 years more than CCI=0) and with a greater percentage of women (45.7% women in CCI≥3 vs. 33.9% in CCI=0).

The analyses report that in-hospital mortality increased with the increasing comorbidity burden. When patients with no comorbidities (CCI=0) were compared to patients with CCI=1, 2 and ≥3, the risk of mortality increased by 31%, 46% and 80% respectively. This result kept consistent with the results of the previous three studies [96, 125, 133] that demonstrated that patients with any comorbidities (CCI>0) had nearly two times the risk of mortality (RR 1.93;

95%CI 1.67–2.24) compared to those with CCI=0 [77]. However, the sample sizes of these studies were smaller compared to this study, lacking generalisability as previously mentioned. Although in my study only in-hospital mortality was evaluated, multiple other studies have shown CCI score to be a predictor of mortality even at one year [54, 96, 134]. In addition, the analyses also included in-hospital MACCE which had limited data in the previous research, a similar pattern of the association between mortality and the comorbid burden was found in MACCE. In this analysis, the most notable of in-hospital complications that increased with increased comorbid burden defined by CCI was the occurrence of acute ischemic stroke and major bleeding. The risk of acute ischemic stroke in CCI≥3 was 2.49 times that in CCI=0. A previous analysis of the NIS database revealed that there was an increase in the incidence of post-PCI ischemic stroke from 2003 to 2016, and post-PCI stroke was associated with significantly higher mortality and increased length of stay [135]. This analysis also showed that there was an increased risk of occurrence of major bleeding complications with the increase in CCI score. It is to be noted that an expert consensus document on high bleeding risk recognizes several of the components of CCI such as advanced age, chronic kidney disease, liver disease, history of stroke or gastrointestinal bleed, as independent risk factors for bleeding following PCI [136], although does not consider measures of overall comorbid burden such as the CCI.

Although increased CCI was associated with adverse outcomes in ACS patients, paradoxically, a notable finding of this study is that ACS patients with severe comorbid burden were more likely to be conservatively treated compared to patients with lesser or no comorbidities. While 72% of patients with no comorbidities underwent angiography, that number was reduced to 47% in those with severe burden. More strikingly only 24% of ACS patients in the severe

group received PCI. One identified study in the systematic review in Chapter 3 based on data analysis of AMI-Florence registry with a smaller sample size (N=740 STEMIs) used the CS method to define the comorbidity burden, it also reported that coronary reperfusion therapy (PCI) was adopted less frequently in higher CS (CS-3(41.9%) than CS-2 (69.4%) or CS-1(78.8%)) [63]. Meanwhile, the same group also demonstrated that PCI reduced one-year mortality with increasing risk profile in ACS patients. It also reported that application of PCI was associated with a long-term survival advantage that increased progressively with increase in risk profile and hypothesized that a conservative approach in these multimorbid patients may not be justified [110]. Patients with severe comorbidity burden are more likely to experience adverse ischemic events and mortality, for example, a previous study with patients who underwent PCI showed that patients with severe comorbid burden were at high risk of major bleeding events, with patients with CCI≥3 having a 4-fold increase in odds of major bleeding complications [108]; in another identified study in my review, Nunez et al. demonstrated that a higher CCI score was an independent predictor of 30-days and one-year of the composite mortality or recurrent AMI [60]. These patients at higher risk of ischemic complications are more likely to benefit from an early invasive approach, but this must be balanced against the increased risk of complications such as major bleeding, stroke and CV complications [108]. A previous study of 1202 ACS patients has shown that addition of CCI to the GRACE score improved the prediction of future CV events and mortality [103], whilst CCI has been shown to be one of the strongest predictors of non-CV mortality in patients undergoing PCI [137]. Incorporation of CCI into risk stratification tools may help guide the management of this complex group of patients.

The analysis for each individual CCI condition suggests that the CCI

components that had the greatest impact on the prognosis of ACS were mainly non- CV conditions that are not routinely included in ACS prognostic scores, such as cancer, moderate or severe liver diseases and peptic ulcer diseases. Among them, it has been proved in a previous study that a diagnosis of current or historical cancer was associated with an increased risk of adverse outcomes among ACS patients [138], where lung cancer being associated with the highest risk of in-hospital mortality, MACCE and stroke, with colon cancer being associated with the highest risk of major bleeding. However, irrespective of cancer type, the presence of metastasis was associated with the worst outcomes.

Finally, it was also reported that comorbidity burden may have an important health economic impact in ACS patients, a gradual increase was observed in the adjusted median cost of hospitalisation in ACS patients with increase in comorbidity burden ($17675 in CCI=0 to $21139 in CCI≥3). As expected, the median length of hospital stay also increased as comorbidity burden increased (5 days for CCI≥3 group, 3 days for CCI=0). In general although length of stay for STEMI patients have been shown to have decreased over time [139], those with a longer hospital stay have been associated with higher morbidity and mortality [140, 141]. An analysis of patients ≥65 years old with STEMI from the CathPCI registry reported that patients with a long length of stay (>5 days) were older, female, had more comorbid conditions including cardiogenic shock and multivessel disease. Previously a study has also demonstrated that among all patients undergoing PCI, CCI score was an independent predictor of length of stay and healthcare costs [108].

5.6 LIMITATIONS

One strength of this study lies in the fact that to my knowledge it is the largest, data up-to-date and most comprehensive study to date evaluating the

impact of comorbidity burden defined by CCI on ACS outcomes and the receipt of invasive strategy. The analysis also reveals that the increasing comorbidity burden of ACS patients over the years and how it impacts the management strategy in terms of a conservative vs. invasive approach. While there have been previous small studies that have evaluated the impact of CCI on ACS patients, they have mostly focused on mortality as an outcome. Unlike the current study, they have failed to comprehensively evaluate the impact of CCI on management strategy and occurrence of complications such as bleeding, stroke, vascular and cardiac complications.

There are several limitations in this study. The analysis categorised CCI scores into an ordinal variable based on the cut-off points used in the CCI paper, which is common in clinical research; useful to label the individual patient as having which level of comorbidity burden; convenient for clinicians to diagnose and manage the patients; and helps for data presentation and interpretation of results. However, categorisation of CCI scores gained at some cost such as losing some statistical power to detect the association between CCI scores and ACS outcomes. However, the sensitivity analysis that conducted CCI scores as a continuous variable has also proved a similar result with the main analysis which is, the increased comorbidity burden defined by CCI was associated with worse ACS. Then, like with any other administrative database, coding errors and underreporting of secondary diagnoses are potential sources of bias [142]. However, the use of ICD-9-CM codes have been previously validated for the purpose of cardiovascular research, and the estimates of hospital characteristics, numbers of discharges, length of stay, and in-hospital mortality from the HCUP NIS for 2007 were highly comparable to three related data sources: the American Hospital Association (AHA) Annual Survey Database; the National Hospital Discharge Survey (NHDS) from the National Center for Health

Statistics; and the MedPAR inpatient data from the Centers for Medicare and Medicaid Services (CMS) [143, 144]. Furthermore, NIS only captures in-hospital outcomes which limit my research to in-hospital events. It is possible that longer-term data on mortality and other adverse events such as major bleeding and further ischemic events may be even greater in patients with a greater comorbid burden. Also, the NIS database lacks formal adjudication of outcomes, and events such as bleeding are not defined based on standardised definitions used in cardiovascular trials [145]. In addition, although the NIS database contains many variables of interest, data on antiplatelet regime type and duration, medical therapy and left ventricular function is not routinely collected and may provide additional information to better stratify risk and procedural outcomes [146]. Finally, in keeping with all observational registry work, the possibility of unmeasured or unrecognized confounders may contribute to the adverse outcomes, although the capture of a wide range of comorbid conditions in the NIS may help to mitigate this bias.

5.7 CONCLUSION

Temporal trends in the demographic and clinical outcomes of ACS patients over the years present an interesting apparent paradox. While in general in-hospital mortality of ACS patients has progressively improved over the years, the level and complexity of comorbid burden among ACS patients has increased, despite greater comorbidity being associated with relatively worse outcomes at the individual level. This cohort of patients with multiple comorbidities poses several challenges from a clinical, financial and healthcare system standpoint [65]. The current study helps establish that this comorbid group of ACS patients is at an increased risk of in-hospital mortality. While this may largely be from the comorbidities themselves and their poor functional and

rehabilitation potential [55], it was hypothesized that lack of aggressive treatment and the reluctance to offer diagnostic angiography and revascularisation also plays a role. Given that patients with a high CCI score are at higher risk of bleeding [108], clinicians must be cognizant of and implement bleeding avoidance strategies in those undergoing PCI [147]. Finally a heart-team model with a multidisciplinary approach (consisting of interventional cardiologist, cardiac surgeon, hospitalist, pharmacist and nurses) plays a vital role in the treatment of these multi-comorbid patients [148, 149]. It not just helps tailor pharmacotherapy and revascularisation to individual patients, but has also been observed to reduce hospitalisations and medical costs, and improve survival [148, 149]. Oftentimes other subspecialists, physical therapists and case managers may need to coordinate care and treat the patient as a whole since comorbidities need to be addressed in parallel rather than in isolation.

Chapter 6 -
Prognostic Impacts of Elixhauser Comorbidity Score on ACS outcomes

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Temporal trends in comorbidity burden and impact on prognosis in patients with acute coronary syndrome using the Elixhauser Comorbidity Index Score

6.1 INTRODUCTION

The previous chapter of this thesis described the temporal trends in CCI comorbidity burden and its impact on ACS prognosis. The current chapter continues to investigate objective two of the thesis by exploring the association of comorbid burden defined by the ECS with the ACS outcomes. The findings from this chapter were published in The American Journal of Cardiology.

While the incidence of ACS has declined in recent years, at least 1 million patients still develop ACS annually in the US [46]. In last chapter that used CCI to define the comorbidity burden, it has stated the importance of studying the prognostic impact of the comorbid burden on ACS outcomes and treatment strategies to guide clinical management (Section 5.1), the prognostic impact of comorbid burden defined by CCI was assessed and it reported a positive association between higher CCI scores and risk of various adverse outcomes in patients with ACS. However, several other studies identified in Chapter 3 have evaluated the prognostic value of other comorbidity measures in ACS patients with some literature indicating that ECS and other comorbidity measures might outperform CCI scores in outcome prediction [82, 83, 99].

The CCI and the ECS are measures of global comorbid burden and have both been widely used to predict prognosis amongst different medical conditions. The modified CCI provides a means of quantifying the prognostic impact of 17 comorbid conditions and has been shown to predict mortality, morbidity, risk of repeat hospitalisations, length of stay and cost of treatment [77]. The modified ECS is another well-validated measure of comorbidity using administrative datasets that has been shown to be superior to CCI in cardiovascular and surgical cohorts [81, 83]. It comprises 30 conditions, each weighted into a single numeric score based on their association with in-hospital

mortality in the original cohort by Van Walraven et al. CCI and ECS are two very different scales both in the numerical sense as well as in the range of comorbidities they comprise. For example, as a result of different comorbidities being included the different measures capture different aspects of comorbidity: ECS (30 comorbidities) has more conditions than CCI (17 comorbidities) and considers non-CV comorbid conditions more broadly including many conditions of mental health, anemia, haematological parameters that are not included in the CCI index but are relatively common. Therefore, the distribution of prevalence of comorbidities in the ACS population would be different, and so examining the profiles of ACS patients under a different comorbidity score is still needed.

However, the findings from the review in Chapter 3 told that most previous studies that explored the impact of comorbidity burden on ACS outcomes used the CCI method to define the comorbidity burden on ACS patients, there is to date no study using the ECS method to define the comorbid burden and report the prognostic impact of comorbid burden in the ACS population. Therefore, the current evidence does not inform physicians of the patterns of comorbidity burden defined by ECS in ACS patients, and whether this burden has changed over time in line with the shift in patient socio-demographics. Furthermore, it is unclear whether there is a difference in the management strategy offered to patients based on the ECS method, and what kind of impact the latter has on clinical outcomes. Therefore, this current chapter aims to explore the above information by using ECS to define the comorbidity burden in ACS patients.

6.2 SPECIFIC OBJECTIVES

The present study was designed to examine national estimates of the

associations between comorbidity burden defined by ECS and in-hospital management strategy and clinical outcomes in patients presenting with ACS in the US. The specific objectives of this chapter were as follows:

I. To study the temporal trends in baseline characteristics, Elixhauser comorbidities, specific conditions, procedures and complications in a large national population admitted with a diagnosis of ACS.
II. To examine how these variables change over the increasing comorbidity burden defined by the ECS in the different patterns.
III. To examine the prognostic impact of comorbidity burden defined by the different patterns of ECS on the ACS outcomes and the receipt of invasive strategies via fitting models.
IV. To visualize the results.

6.3 METHODS

6.3.1 Data Processing

This chapter also has a specific goal and requires a targeted processing based on the original dataset. A brief summary of the data processing for the ECS chapter is provided here.

In the CCI chapter, all treatment, secondary and clinical complications variables were extracted, additionally, not like CCI comorbidities, the NIS database has contained all 29 ECS comorbidities (except cardiac arrhythmias) which are needed in this chapter. Cardiac arrhythmias was excluded in the NIS database and also supported by clinicians since it may have been present on admission (i.e. comorbidity) or occurred as a result of ACS (i.e. outcome). Hence, only three ECS score variables need to be generated. Each of the ECS comorbidities was weighted into a single numeric score based on their association with in-hospital mortality in the original cohort by Van Walraven et

al (**Appendix Table 6.1**). A ECS continuous variable was created based on this weight system via summing up scores of these 29 comorbidities into a total score, with a possible range of scores between -19 and +89. Then, according to the method of cut-off values in the Elixhauser paper [73], total ECS was stratified in to 5 groups for the purpose of analysis; <0, 0, 1-5, 6-13, ≥14. The number of Elixhauser comorbidities (NEC) was also calculated by summing individual comorbidities and stratified into 6 groups; 0, 1, 2, 3, 4 and ≥5 comorbidities. Finally, based on the original dataset, a new dataset was generated including one continuous ECS scores and two categorical ECS scores.

6.3.2 Study Design and Outcomes

Patient-level variables were already available in the NIS database including age, gender, race, admission day (weekday versus weekend), median household income and patient Elixhauser comorbidities described by Van Walraven et al. Other clinically relevant comorbidities (smoking, atrial fibrillation, long-term use of anticoagulants, dementia, previous MI, previous PCI, and prior CABG), procedural characteristics such as PCI, CA, thrombolysis, CABG, use of IABP.

The primary outcomes of interest (in-hospital mortality, MACCE and major bleeding) and secondary outcomes (the receipt of invasive management (PCI or CA), length of stay and total cost of hospitalisation) were the same as the CCI chapter.

6.3.3 Statistical Analysis

Statistical analyses were performed using STATA version 14.0. OR and their corresponding 95%CI were used to report the results of models. In this chapter, since hospitals sampled records rather than individuals, each hospital was defined as primary sampling unit in the survey estimation. I continued

using survey estimation commands due to the complex survey design via applying the sampling weights provided by the AHRQ to produce national estimates. Apart from the temporally descriptive information for variables displayed in the CCI chapter, descriptive statistics was added for 29 ECS comorbidities and ECS score variables in this chapter. Trend analyses for all baseline information of patients stratified by ECS and NEC were also conducted. On the basis of the imputation processing in the CCI chapter, the ECS score variable was added into the imputation models in this chapter, with the number of imputation datasets equal to the highest proportion of missing in any variables.

Multivariable logistic models using maximum likelihood estimation were fitted to investigate the association of comorbid burden defined by ECS and NEC with in-hospital outcomes and the receipt of invasive management. The following variables selected in Section 6.3.2 were added in the models for adjustment: age, gender, race, median ZIP income, day of admission, smoking status, diagnosis of atrial fibrillation, long-term use of anticoagulants, dementia, previous MI, prior PCI, prior CABG, use of PCI, CA or CABG, use of IABP, infusion of thrombolytic agent during admission and year of hospitalisation. The lowest score groups "ECS<0" and "NEC=0" were used as the reference category for analyses, respectively. Exploratory analyses based on medians were conducted to see the impact of the comorbid burden on length of in-hospital stay and total charge.

Sensitivity analyses using the ECS score and NEC score as continuous variables were conducted to assess the impact of the per-unit score of ECS and NEC on in-hospital outcomes (MACCE, mortality, acute stroke and major bleeding).

6.4 RESULTS

The process of excluding data was the same as the CCI chapter (**Appendix Figure 5.1**), but with ECS score variables added in. Similarly, a total of 7,201,900 weighted records (1,499,142 unweighted) with a principal diagnosis with ACS were included in the final dataset.

In addition to the basic information of demographics in the CCI chapter, descriptive statistics over the study years of ECS comorbidities, ECS scores and NEC scores before multiple imputations are listed in **Appendix Table 6.2**. The median age of the total cohort was 67 (56-79) years old with 40% females. Among the 29 ECS comorbidities, it was observed a significant rise in the prevalence of some CV risk factors such as diabetes (complicated and uncomplicated), hypertension, and renal failure. The overall comorbidity burden increased over the 11-year period, with higher ECS (ECS=6-13, ECS≥14) and NEC (NEC 4 and 5) groups becoming more prevalent in later years (ECS: 2004 to 2014: 13.1% to 19.2%, and 2.1% to 4.6%, respectively; NEC=4: 8% to 14%, and NEC≥5: 4% to 16%) while there was a reduction from 15% to 7% in the proportion of patients with no comorbidities over 11 years. **Figures 6.1** illustrates how the comorbid burden has changed over the study years based on the ECS and NEC.

The distribution of ECS and NEC groups among the whole dataset is illustrated in **Figure 6.2**. ECS=0 category had the highest proportion of patients (37.6%), while only 3.5% of the patients had an ECS≥14. Within the NEC groups, more than a quarter of patients had two comorbidities (25.2%), closely followed by patients with one comorbidity (23.1%). Several differences in patient characteristics were observed between the ECS groups as well as the NEC groups (**Tables 6.1**). The average age increased with comorbidity burden in both the ECS and NEC groups. A minimal difference in sex distribution was observed

within the ECS groups, with males being more prevalent across all groups. In contrast, males were more prevalent in the lower NEC groups whereas an equal sex distribution was observed in those with 5 or more comorbidities (NEC≥5). The prevalence of some CV risk factors increased in parallel to NEC class (NEC 1 to 5: hypertension 57.8% to 89.8%, diabetes uncomplicated 8.1% - 48.4%, diabetes with complications 0.8% to 21.8%, obesity 3.2% - 27.0%). In contrast, in the ECS groups, the highest prevalence of CV comorbidities was in ECS<0 groups while the lowest was in ECS=0.

6.4.1 Management Strategy

It was observed that the proportions of patients in higher ECS and NEC groups who underwent CA or PCI (**Tables 6.1**) were lower than that of those in the lowest comorbidity burden groups (PCI: 45.3% in ECS<0 vs 18.6% in ECS≥14; 57.4% in NEC=0 vs 24.4% in NEC≥5. CA: 69.3% in ECS<0 to 38.2% in ECS≥14; 73.4% in NEC=0 vs 49.3% in NEC≥5). In contrast, there was no difference in rates of CABG between ECS groups whereas the CABG rates were significantly higher in patients with a greater number of comorbidities.

In multivariable analysis, higher ECS was associated with decreased odds of PCI and CA, except the ECS=0 group. For example, patients with the highest ECS comorbidity burden (ECS≥14) were 65% less likely in the odds of receiving a PCI compared to those with ECS<0 (OR 0.35, 95% CI 0.34-0.36). When patients were stratified by NEC, higher NEC was associated with a lower odd of receiving PCI and CA. In comparison to patients with no comorbidities (NEC=0), patients in NEC=4 and ≥5 were 46% and 55% less likely in the odds of receiving a CA (OR 0.54, 95%CI 0.52-0.57 in NEC=4; OR 0.45, 95%CI 0.43-0.47 in NEC≥5). Other outcomes are listed in **Table 6.3**.

Figure 6.1: Distribution of the ECS and NEC groups across the study years (2004-2014).

Table A for ECS:

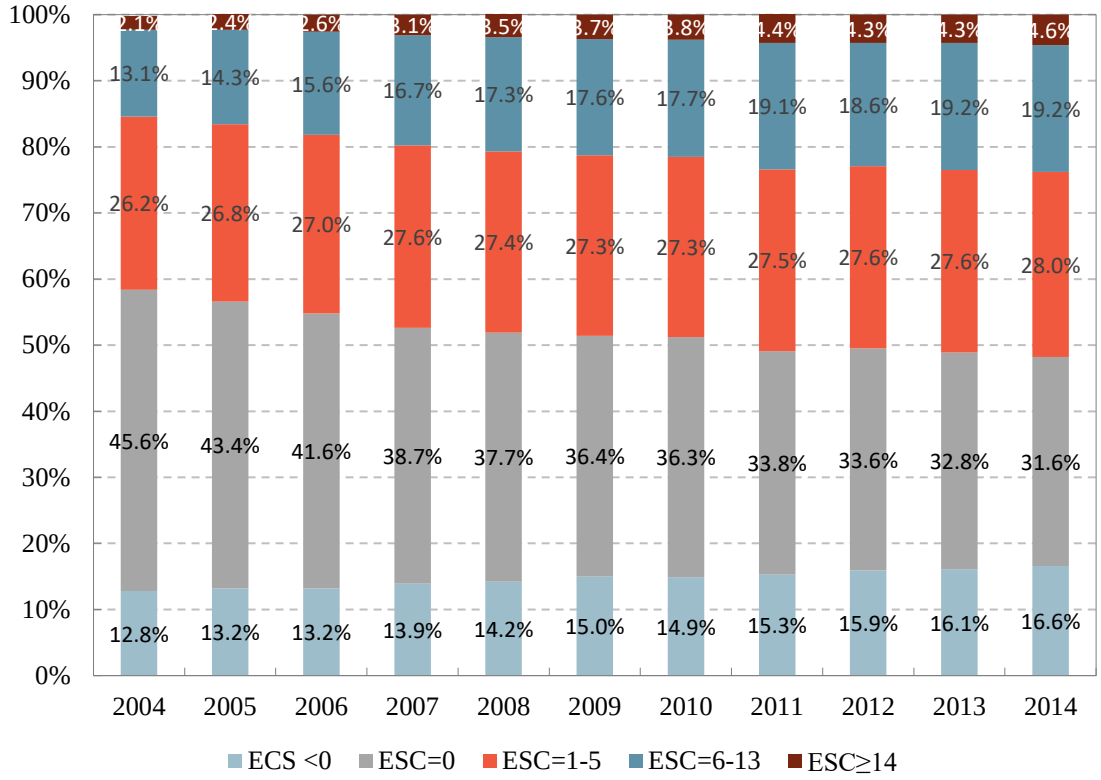


Table B for NEC:

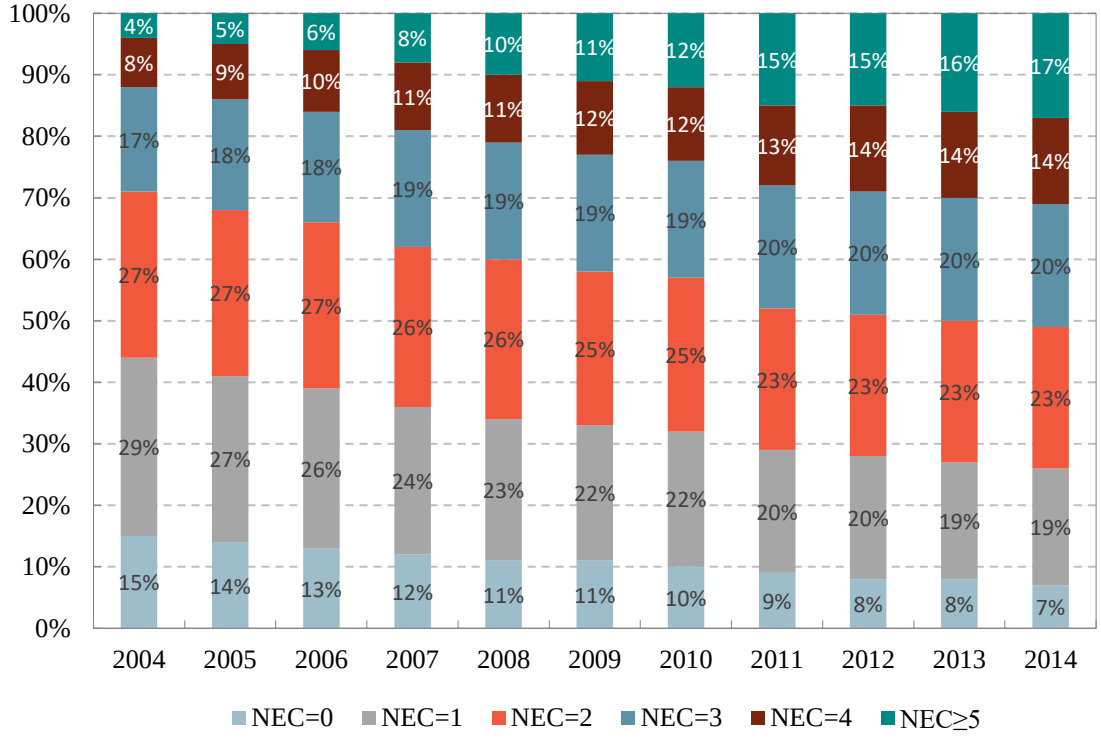


Figure 6.2: Distribution of comorbidity burden according to ECS and NEC categories.

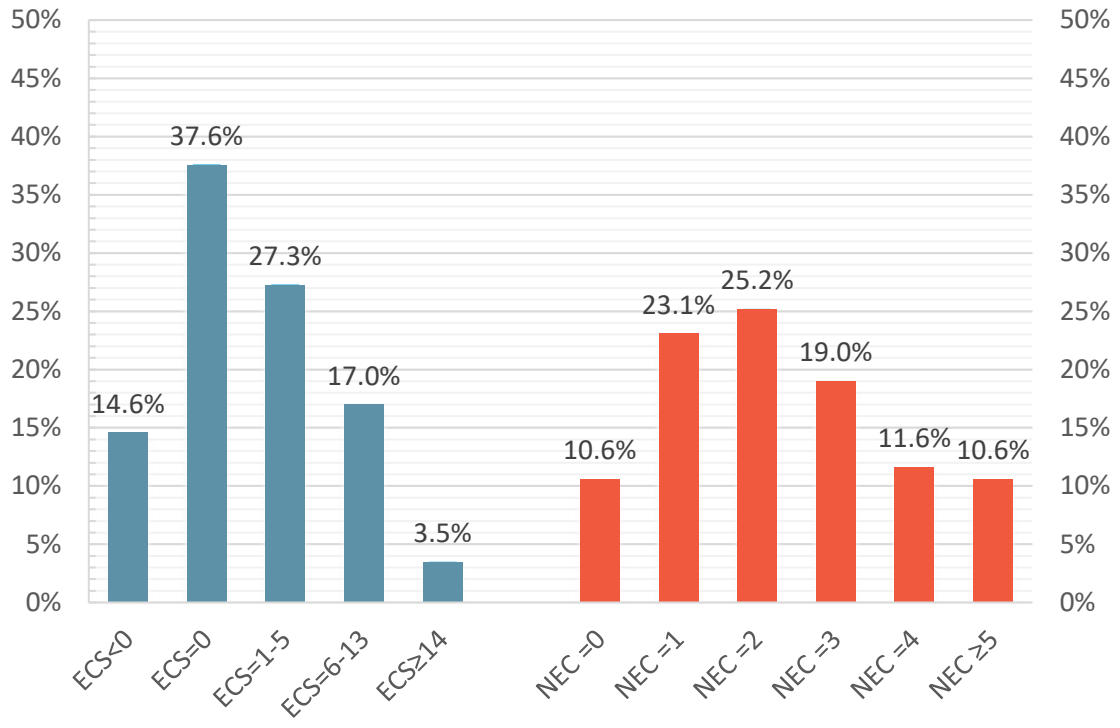


Table 6.1: Patient and procedural characteristics stratified by categorised Elixhauser Comorbidity Index Score (ECS) and categorised Number of Elixhauser Comorbidities (NEC).

Table A for ECS:

	Elixhauser Comorbidity Index Score (ECS)				
	ECS<0	**ECS=0**	**ECS=1-5**	**ECS=6-13**	**ECS≥14**
Patient demographics, %					
Group % (no. of weighted discharges)	14.6% (1,050,655)	37.6% (2,711,226)	27.3% (1,963,794)	17.0% (1,224,718)	3.5% (251,506)
Median age, years (IQR)	60 (51-72)	63 (53-75)	71 (60-81)	75 (64-83)	74 (64-82)
Female, %	44.0%	33.9%	43.9%	44.9%	42.3%
Race, %					
White	62.1%	62.3%	63.8%	64.0%	63.6%
black	10.5%	6.5%	8.5%	9.3%	11.0%
Hispanic	6.8%	6.4%	5.8%	6.2%	6.9%
Asian/Pacific islander	1.1%	2.0%	1.8%	2.0%	2.4%
Native American	0.5%	0.4%	0.5%	0.5%	0.5%
other	2.5%	3.0%	2.4%	2.3%	2.5%

	Elixhauser Comorbidity Index Score (ECS)				
	ECS<0	**ECS=0**	**ECS=1-5**	**ECS=6-13**	**ECS≥14**
Missing Race	16.4%	19.2%	17.2%	15.7%	13.2%
Weekend admission, %	26.2%	25.6%	25.7%	26.0%	26.0%
Median zip code income national quartile, %					
Frist	30.4%	27.0%	30.0%	30.3%	30.9%
Second	27.4%	27.1%	27.8%	27.3%	26.4%
Third	23.5%	24.1%	23.2%	23.1%	23.3%
Fourth	18.7%	21.8%	19.1%	19.3%	19.5%
Elixhauser Comorbidity, %					
Congestive heart failure	0.0%	0.0%	0.2%	2.5%	10.3%
Valvular disease	0.2%	0.0%	0.1%	0.7%	2.3%
Pulmonary circulation Disorders	0.0%	0.0%	0.0%	0.2%	1.6%
Peripheral vascular disorders	4.4%	1.1%	18.7%	20.7%	23.6%
Hypertension	70.8%	61.5%	68.9%	69.2%	67.6%
Paralysis	0.0%	0.0%	0.5%	5.6%	13.6%
Other neurologic disorder	0.5%	0.1%	2.5%	22.3%	31.7%
Chronic pulmonary disease	12.0%	1.6%	36.5%	38.9%	45.4%
Diabetes uncomplicated	35.6%	23.9%	29.5%	28.7%	26.8%
Diabetes with chronic complications	5.2%	2.0%	7.5%	11.0%	11.9%
Hypothyroidism	10.0%	7.5%	10.6%	12.0%	11.6%
Renal failure	2.3%	0.3%	22.5%	43.6%	54.0%
Liver disease	0.0%	0.0%	0.2%	2.9%	17.8%
Peptic ulcer disease excluding bleeding	0.05%	0.03%	0.04%	0.04%	0.05%
AIDS/HIV	0.2%	0.1%	0.1%	0.2%	0.3%
Lymphoma	0.0%	0.0%	0.1%	1.6%	5.5%
Metastatic cancer	0.0%	N/A	0.0%	1.8%	14.9%

	Elixhauser Comorbidity Index Score (ECS)				
	ECS<0	**ECS=0**	**ECS=1-5**	**ECS=6-13**	**ECS≥14**
Solid tumour without metastasis	0.1%	0.1%	1.9%	3.8%	5.2%
Rheumatoid arthritis/collagen vascular diseases	2.2%	1.7%	2.4%	2.4%	2.2%
Coagulopathy	1.2%	0.1%	4.7%	11.1%	21.3%
Obesity	56.0%	0.2%	8.9%	5.6%	3.5%
Weight loss	0.1%	0.0%	0.5%	6.0%	25.1%
Fluid and electrolyte disorders	2.6%	0.2%	26.9%	48.8%	67.9%
Chronic Blood loss anemia	2.1%	0.1%	1.3%	1.6%	1.8%
Deficiency anemias	26.4%	1.4%	17.7%	23.8%	27.2%
Alcohol abuse	4.3%	2.0%	2.6%	2.9%	5.8%
Drug abuse	11.5%	0.1%	0.7%	0.6%	0.6%
Psychoses	2.7%	1.3%	2.2%	2.9%	3.6%
Depression	21.7%	2.1%	5.5%	4.9%	4.3%
Other conditions, %					
Smoking	40.8%	35.4%	33.7%	26.5%	25.0%
Atrial Fibrillation	12.0%	11.7%	19.7%	24.6%	26.6%
Long-term AC use	2.6%	2.2%	3.4%	3.7%	3.3%
Dementia	1.1%	1.0%	2.8%	10.0%	11.6%
Previous MI	10.5%	9.0%	11.3%	11.0%	9.5%
Previous PCI	12.3%	11.3%	11.9%	10.1%	8.1%
Previous CABG	5.8%	6.2%	8.9%	9.3%	7.6%
Treatments/procedural characteristics, %					
PCI	45.3%	52.3%	35.0%	24.8%	18.6%
CA	69.3%	70.7%	58.6%	46.7%	38.2%
Infusion of thrombolytic agent	1.4%	1.7%	1.1%	0.9%	0.8%
CABG	9.8%	6.0%	9.8%	10.0%	10.0%
IABP use	3.8%	3.7%	5.1%	5.8%	6.7%
Resource utilisation (Median/IQR)					
Median (IQR) length of stay (LOS), d	3 (2-5)	3 (2-4)	4 (2-6)	5 (3-9)	6 (3-12)

	Elixhauser Comorbidity Index Score (ECS)				
	ECS<0	**ECS=0**	**ECS=1-5**	**ECS=6-13**	**ECS≥14**
Median (IQR) adjusted cost of hospitalisation, $	$18371.5 (14683-23358)	$16762.2 (14026-21435)	$19632.6 (14088-24360)	$23114.6 (14451-27419)	$31332.3 (16639-35047)

Table B for NEC:

	Number of Elixhauser Comorbidities					
	NEC=0	**NEC=1**	**NEC=2**	**NEC=3**	**NEC=4**	**NEC≥5**
Patient demographics, %						
Group % (no. of weighted discharges)	10.6% (763,385)	23.1% (1,663,327)	25.2% (1,813,077)	19.0% (1,366,638)	11.6% (832,517)	10.6% (762,957)
Median (IQR) age, y	59 (50-71)	64 (54-77)	68 (57-79)	70 (59-81)	72 (61-81)	72 (62-81)
Female, %	26.2%	33.7%	40.6%	45.5%	48.0%	50.0%
Race, %						
White	64.0%	63.1%	62.1%	62.6%	63.1%	64.7%
black	4.2%	6.5%	8.1%	9.5%	10.7%	11.7%
Hispanic	5.2%	5.6%	6.3%	6.4%	6.9%	8.0%
Asian/Pacific islander	1.8%	1.8%	1.8%	1.8%	1.9%	2.3%
Native American	0.4%	0.4%	0.5%	0.5%	0.5%	0.6%
other	2.9%	2.8%	2.7%	2.5%	2.5%	2.5%
Missing Race	21.3%	19.7%	18.5%	16.8%	14.5%	10.3%
Weekend admission, %	26.0%	25.8%	25.7%	25.8%	25.7%	25.7%
Median zip code income national quartile, %						
Frist	24.6%	26.9%	29.4%	30.6%	31.1%	31.5%
Second	27.1%	27.3%	27.5%	27.5%	27.4%	27.1%
Third	24.6%	24.2%	23.3%	23.0%	23.0%	23.4%
Fourth	23.7%	21.7%	19.8%	18.9%	18.4%	18.0%
Elixhauser Comorbidity, %						
Congestive heart failure	N/A	0.2%	0.4%	0.8%	1.4%	3.7%
Valvular disease	N/A	0.0%	0.1%	0.2%	0.4%	1.3%
Pulmonary circulation Disorders	N/A	0.0%	0.0%	0.1%	0.1%	0.7%

	Number of Elixhauser Comorbidities					
	NEC=0	**NEC=1**	**NEC=2**	**NEC=3**	**NEC=4**	**NEC≥5**
Peripheral vascular disorders	N/A	2.1%	6.9%	13.1%	20.0%	32.9%
Hypertension	N/A	57.8%	73.3%	80.4%	85.0%	89.8%
Paralysis	N/A	0.3%	0.9%	1.8%	3.0%	5.7%
Other neurologic disorder	N/A	1.6%	4.2%	7.2%	10.2%	15.7%
Chronic pulmonary disease	N/A	7.5%	17.7%	27.5%	36.0%	46.7%
Diabetes uncomplicated	N/A	8.1%	30.7%	41.9%	46.4%	48.4%
Diabetes with chronic complications	N/A	0.8%	2.9%	6.6%	11.9%	21.8%
Hypothyroidism	N/A	2.7%	7.6%	12.7%	17.3%	25.1%
Renal failure	N/A	1.2%	6.9%	19.1%	35.3%	58.2%
Liver disease	N/A	0.2%	0.6%	1.2%	2.2%	4.6%
Peptic ulcer disease excluding bleeding	N/A	0.0%	0.0%	0.1%	0.1%	0.1%
AIDS/HIV	N/A	0.1%	0.1%	0.1%	0.2%	0.4%
Lymphoma	N/A	0.2%	0.3%	0.6%	0.9%	1.3%
Metastatic cancer	N/A	0.3%	0.6%	1.1%	1.6%	2.1%
Solid tumor without metastasis	N/A	0.4%	1.1%	1.8%	2.6%	3.7%
Rheumatoid arthritis/collagen vascular diseases	N/A	0.7%	1.7%	2.8%	3.9%	5.4%
Coagulopathy	N/A	0.9%	2.4%	4.5%	7.6%	14.7%
Obesity	N/A	3.2%	9.9%	17.4%	20.4%	27.0%
Weight loss	N/A	0.3%	0.8%	1.9%	3.8%	9.1%
Fluid and electrolyte disorders	N/A	5.1%	13.0%	23.0%	34.7%	53.4%
Chronic Blood loss anemia	N/A	0.3%	0.7%	1.3%	2.0%	3.2%
Deficiency anemias	N/A	2.1%	6.8%	15.8%	30.0%	52.6%

	Number of Elixhauser Comorbidities					
	NEC=0	**NEC=1**	**NEC=2**	**NEC=3**	**NEC=4**	**NEC≥5**
Alcohol abuse	N/A	1.0%	2.6%	3.7%	4.7%	6.2%
Drug abuse	N/A	1.0%	1.9%	2.6%	3.2%	4.2%
Psychoses	N/A	0.5%	1.3%	2.5%	3.9%	6.7%
Depression	N/A	1.6%	4.5%	8.2%	11.9%	18.8%
Other conditions, %						
Smoking	39.3%	36.0%	33.2%	31.9%	31.4%	31.2%
Atrial Fibrillation	9.6%	13.3%	16.1%	18.7%	21.1%	23.6%
Long-term AC use	1.6%	2.3%	2.8%	3.3%	3.8%	4.0%
Dementia	0.6%	1.5%	2.9%	4.4%	5.8%	7.2%
Previous MI	5.9%	8.9%	10.1%	11.2%	12.3%	13.6%
Previous PCI	7.4%	10.8%	11.5%	12.1%	12.6%	13.0%
Previous CABG	3.7%	5.8%	7.4%	8.7%	9.6%	10.6%
Treatments/procedural characteristics, %						
PCI	57.4%	50.3%	41.9%	34.5%	28.9%	24.4%
CA	73.4%	69.2%	63.2%	57.7%	53.0%	49.3%
Infusion of thrombolytic agent	2.0%	1.6%	1.3%	1.1%	1.0%	0.9%
CABG	5.1%	6.7%	8.2%	9.5%	10.4%	11.6%
IABP use	4.7%	4.3%	4.3%	4.5%	4.7%	5.4%
Resource utilisation (Median/IQR)						
Median (IQR) length of stay (LOS), days	2 (2-4)	3 (2-4)	3 (2-5)	3 (2-6)	4 (2-7)	5 (3-9)
Median (IQR) adjusted cost of hospitalisation, $	$17362 (14501 - 21632)	$17630 (14226-22085)	$18188 (14819-22572)	$19384 (14960-23822)	$21193 (15269 - 25664)	$25924 (16394 - 31146)

AC: Anticoagulants; ACS: acute coronary syndrome; IQR: interquartile range; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; IABP: intra-aortic balloon pump; MI: myocardial infarction.

6.4.2 Clinical Outcome

There was an incremental rise in MACCE and mortality events with increasing ECS and NEC classes (MACCE: 3.8% in ECS<0 to 22.2% in ECS≥14, 5.6% in NEC=0 to 12.2% in NEC≥5; mortality: 2.0% in ECS<0 to 15.8% in

ECS≥14, 3.8% in NEC=0 to 8.5% in NEC≥5) (**Tables 6.2**). The lowest incidence of complications (acute stroke, vascular complications and major bleeding) was observed in the ECS group (ECS=0) with a rise in complication rates with increasing ECS scores. For example, the proportion of major bleeding in ECS=0 was the lowest (3.1%), then increased to 10.0% in ECS≥14. A similar pattern was observed in NEC groups.

In multivariable analysis (**Table 6.3**), higher ECS was independently associated with increased odds of MACCE and mortality compared to ECS<0 group. ECS≥14 had over 4-fold increase in the odds of MACCE and mortality (OR 4.66, 95%CI 4.50-4.82 and OR 4.86, 95%CI 4.65-5.07, respectively), compared to ECS<0 group, with groups similarly associated with increased odds of MACCE and mortality (ECS 0, ECS 1-5 and ECS 6-13). The odds of acute ischemic stroke and major bleeding increased with rising ECS, except ECS=0 group where there was no increased risk of stroke (OR 0.98, 95%CI 0.92-1.03) or major bleeding (OR 0.62, 95%CI 0.59-0.64) compared to those with a score of <0. Within the NEC groups, a higher NEC count was associated with increased odds of MACCE and in-hospital mortality compared to those without comorbidities (NEC=0), with the exception of patients with only one comorbidity (NEC=1) who were at no increased risk of either event. Higher NEC count was also associated with increased odds of acute ischemic stroke and major bleeding in all groups compared to those without comorbidities, with NEC≥5 being associated with 2-3-fold higher odds of either complication (stroke: OR 3.07 95%CI 2.82-3.34 and major bleeding: OR 2.56 95%CI 2.44-2.70).

Table 6.2: In-hospital clinical outcomes by categorised Elixhauser Comorbidity Index Score (ECS) and categorised Number of Elixhauser Comorbidities (NEC).

	Elixhauser Comorbidity Index Score (ECS)				
Outcomes	**ECS<0**	**ECS=0**	**ECS=1-5**	**ECS=6-13**	**ECS≥14**

MACCE	3.8%	4.6%	8.6%	14.6%	22.2%
Mortality	2.0%	2.9%	6.3%	10.9%	15.8%
Acute ischemic stroke	0.8%	0.7%	1.5%	3.3%	6.5%
Major Bleeding	4.4%	3.1%	5.4%	6.9%	10.0%

	Number of Elixhauser Comorbidities (NEC)					
Outcomes	**NEC=0**	**NEC=1**	**NEC=2**	**NEC=3**	**NEC=4**	**NEC≥5**
MACCE	5.6%	6.1%	7.3%	8.6%	10.0%	12.2%
Mortality	3.8%	4.1%	5.0%	6.1%	7.2%	8.5%
Acute ischemic stroke	0.7%	1.0%	1.4%	1.9%	2.2%	3.0%
Major Bleeding	3.4%	3.8%	4.4%	5.1%	6.0%	7.5%

MACCE: major acute cardiovascular and cerebrovascular events: composite of death, cardiac complications, stroke, and vascular complications.

Table 6.3: Association of categorised van Walraven Elixhauser index scores and categorised number of Elixhauser comorbidities with in-hospital clinical outcomes with ACS diagnosis (adjusted odds ratio, 95% confidence intervals † §).

	Elixhauser Comorbidity Index Score (ECS)			
Outcomes*	**ECS =0**	**ECS =1-5**	**ECS =6-13**	**ECS ≥14**
PCI†	1.34 (1.31, 1.40)	0.81 (0.79, 0.83)	0.55 (0.54, 0.56)	0.35 (0.34, 0.36)
CA†	1.24 (1.21, 1.27)	0.84 (0.82, 0.85)	0.58 (0.57, 0.59)	0.37 (0.36, 0.38)
MACCE§	1.12 (1.08, 1.15)	1.80 (1.75, 1.85)	2.86 (2.79, 2.94)	4.66 (4.50, 4.82)
Mortality§	1.26 (1.21, 1.30)	2.16 (2.08, 2.23)	3.30 (3.18, 3.42)	4.86 (4.65, 5.07)
Acute ischemic stroke§	0.98 (0.92, 1.03)	1.50 (1.42, 1.59)	3.07 (2.89, 3.26)	6.16 (5.76, 6.58)
Major Bleeding§	0.62 (0.59, 0.64)	1.11 (1.08, 1.14)	1.48 (1.44, 1.53)	2.32 (2.22, 2.42)

	Number of Elixhauser Comorbidities (NEC)

Outcomes**	NEC=1	NEC=2	NEC=3	NEC=4	NEC≥5
PCI†	0.90 (0.89,0.92)	0.72 (0.71,0.74)	0.56 (0.55,0.58)	0.44 (0.43,0.46)	0.35 (0.34,0.37)
CA†	0.97 (0.94,0.99)	0.81 (0.78,0.83)	0.66 (0.64,0.69)	0.54 (0.52,0.57)	0.45 (0.43,0.47)
MACCE§	0.97 (0.95,1.00)	1.08 (1.05,1.12)	1.23 (1.18,1.27)	1.38 (1.32,1.43)	1.70 (1.64,1.77)
Mortality§	0.94 (0.91,0.97)	1.03 (1.01,1.06)	1.16 (1.11,1.20)	1.30 (1.25,1.36)	1.57 (1.50,1.64)
Acute ischemic stroke§	1.29 (1.19,1.39)	1.66 (1.54,1.79)	2.03 (1.87,2.20)	2.36 (2.17,2.56)	3.07 (2.82,3.34)
Major Bleeding§	1.12 (1.08,1.16)	1.31 (1.25,1.37)	1.57 (1.50,1.65)	1.92 (1.83,2.02)	2.56 (2.44,2.70)

*Reference is ECS<0; **Reference is NEC=0.

ACS: acute coronary syndrome; PCI: percutaneous coronary intervention; CA: coronary angiography; MACCE: major acute cardiovascular and cerebrovascular events: composite of death, cardiac complications, stroke, and vascular complications.

† Adjustment for age, gender, ethnicity, day of admission (weekday/weekend), median income, type of ACS, If the patient smokes, diagnosis of dementia, diagnosis of atrial fibrillation, long-term use of anticoagulants, previous diagnosis of myocardial infarction, previous procedure of percutaneous coronary intervention, previous procedure of coronary artery bypass graft, use of intra-aortic balloon pump, infusion of thrombolytic agent and year of hospitalisation.

§ Adjustment for age, gender, ethnicity, day of admission (weekday/weekend), median income, If the patient smokes, diagnosis of dementia, diagnosis of atrial fibrillation, long-term use of anticoagulants, previous diagnosis of myocardial infarction, previous procedure of percutaneous coronary intervention, previous procedure of coronary artery bypass graft, use of percutaneous coronary intervention, coronary angiography, coronary artery bypass graft, use of intra-aortic balloon pump, infusion of thrombolytic agent and year of hospitalisation.

The prognostic association of each individual Elixhauser component on clinical outcomes was given in **Appendix Table 6.3**. As a sensitivity analysis, the association between in-hospital outcomes and ECS and NEC scores as continuous variables was undertaken. It was observed that a 1-unit increase in either score was independently associated with increased odds of all adverse outcomes (**Appendix Table 6.4**). For example, per one unit increase in ECS and NEC was associated with about a 1.1-fold increase in the odds of mortality (ECS: OR 1.084 95%CI 1.082-1.086; NEC: OR 1.10, 95%CI 1.09-1.11).

6.4.3 Length of Stay and Cost

Then median length of stay increased in patients with an ECS>0: (ECS <0 and ECS=0: 3 days, ECS=1-5: 4 days, ECS=6-13: 5 days, ECS≥14: 6 days) **(Table 6.1).** Similarly, patients with no comorbidity (NEC=0) had 2 days in hospital, those with 1,2,3 comorbidities had same median length of stay (3 days), 4 days for those with 4 comorbidities, 5 days for those with more than 5 comorbidities**.** Patients with ECS=0 had the lowest median adjusted cost of hospitalisation ($16,762). Adjusted cost of hospitalisation increased gradually with increasing number of comorbidities ($17362 in NEC=0 vs. $25924 in NEC≥5).

6.5 DISCUSSION

It presents a large study to examine temporal trends of comorbidity burden defined by ECS in patients with ACS from a national perspective and report several important findings. First, it shows an increasing burden of comorbidity even defined by ECS in patients presenting with ACS over an 11-year period. From 2004 to 2014, the proportion presenting with an ACS having 5 or more ECS comorbidities increased from 4% to almost one in five patients.

It demonstrates an association between the number and severity of ECS comorbidities and ACS-related adverse outcomes, including MACCE, mortality, acute ischemic stroke and major bleeding, which persisted despite adjustment for differences in receipt of invasive management.

CCI analysis revealed that some CCI comorbidities such as the history of previous MI, diabetes and its chronic complications and previous CVD are increasing while this analysis reported that a significant rise in the prevalence of some ECS comorbidities such as not only diabetes (complicated and uncomplicated), but also hypertension, and renal failure. Previous studies were focused to use CCI on the measurement of comorbid burden and report the epidemiological information of CCI comorbidities [122, 132], there is limited data on how ECS comorbidities and comorbid burden measured by ECS change over time and their distribution in ACS patients.

The CCI chapter has mentioned that previous studies have examined the association between comorbidity burden and ACS outcomes. However, their findings have been subject to limitations as previously described, making them less generalizable to the target population. Furthermore, the majority of studies have assessed comorbidity using CCI instead of ECS, despite the latter being more superior in predicting mortality in cardiovascular cohorts, and did not examine outcomes other than mortality in the ACS population. A two-centre study of 5275 AMI patients hospitalized in Spain between 2003 and 2009 reported a rise in the incidence of AMI and number of comorbidities over the study period, it also showed that increased odds of mortality was associated with per unit increase number of Elixhauser (OR 1.14, 95% CI 1.07-1.22) and per unit score increase of Charlson indices (OR 1.17, 95% CI 1.11-1.23) [101]. However, the study did not examine the impact of comorbidity on management strategy and clinical outcomes such as bleeding, vascular and cardiac

complications and stroke. In a meta-analysis of studies examining the effect of comorbidity, as measured by CCI, on ACS outcomes, each additional unit of CCI score was associated with a 33% increased risk of mortality (RR 1.33, 95% CI 1.15-1.54) and a higher CCI score was shown to correlate with increased odds of in-hospital, 30-day and 6-month mortalities [77]. However, CCI and ECS are two different scales both in numerical sense and in the scoring systems. Apart from what I mentioned above, the two measures cover different aspects of comorbidity, additionally, it is very likely that they highlight different populations as being the same level of comorbid burden. Therefore, it is of the same importance of assessing the impact of comorbid burden defined by ECS on ACS prognosis. The ECS analysis highlights the impact of comorbidity burden defined by Elixhauser, including severity and number, on all major ACS-related outcomes and report a "dose-response" relationship between comorbidity burden and these outcomes. Higher ECS and NEC groups were associated with a significantly increased risk of mortality, acute ischemic stroke, major bleeding and MACCE. Moreover, each additional ECS unit score or comorbidity count (NEC) was associated with an increased risk of all complications. Although these findings may in part be due to lower rates of coronary revascularization in these patients, comorbidity itself was shown to be an independent predictor of adverse outcomes.

Only a few studies have examined the impact of comorbidity burden on receipt of invasive management in patients with ACS. A study of 740 patients with STEMI reported lower rates of coronary reperfusion (primary PCI or thrombolysis) in those with a higher chronic comorbidity score [63]. While this study provides us with insights into the invasive management (or lack thereof) of a specific subgroup of AMI, in a modest number of patients, my analysis confirms that this finding is consistent nationwide in both STEMI and NSTEMI

subgroups. It was observed an inverse relationship between comorbidity severity (ECS) and number (NEC) and receipt of CA and PCI, especially in patients with ECS≥14 and NEC≥5 who were 30-50% less likely than ECS<0 and NEC=0 groups, respectively, to receive either procedure. This result extended the results in the previous CCI analysis that patients with severe comorbidity burden were less likely to receive invasive management (PCI and CA). Interestingly, while the severity of comorbidity burden had no impact on the rates of receipt of CABG, the number of comorbidities was positively associated with the receipt of CABG. The latter is likely due to the characteristics of patients with multiple comorbidities, who were older and had a higher prevalence of diabetes, both of which favouring CABG over PCI for reduction of long-term mortality, re-infarction and need for repeat revascularisation [150, 151].

6.6 LIMITATIONS

To the best of my knowledge, this ECS analysis is the first study to provide a comprehensive illustration of the association between the comorbidity burden defined by the ECS and the ACS outcomes and the receipt of invasive strategy in a national healthcare system. Unlike the CCI measure, there was limited data about using ECS measure to investigate the ACS prognosis and the management, as well as reported their estimates. This ECS analysis reveals that the increasing comorbidity burden defined by ECS in ACS patients was associated with poorer outcomes and lower utilisations of the management strategy. However, certain limitations should be considered whilst interpreting these observations. Given that the ECS analysis used the same data source as the CCI chapter, the limitations of the NIS database existing in ECS analysis are the same as the CCI chapter. Furthermore, like the CCI analysis, the ECS analysis also categorised ECS scores into an ordinal variable, which might cause

information loss in the investigation of the association. However, the cut-off points used in this ECS analysis were based on the original ECS paper and were also used in other versions of ECS measures. Also, a sensitivity analysis was also performed that conducted ECS scores as a continuous variable and it proved a similar result with the main analysis. However, the possibility of a non-linear association of the continuous ECS scores with ACS outcomes was not investigated furtherly.

6.7 CONCLUSION

This nationwide analysis of more than 7 million ACS hospitalisations demonstrates an inverse relationship between the number and severity of comorbidities and receipt of invasive strategies such as CA and PCI, but not CABG, which was more utilised in patients with a higher number of comorbidities. Furthermore, it showed that a greater comorbidity burden as measured by either Elixhauser score or the number of comorbidities correlates with worse clinical outcomes, including mortality, bleeding and stroke. The present study emphasizes the importance of objective comorbidity burden assessment to guide to management strategy and reliably assess prognosis at an individual patient level.

Chapter 7 -
Comparative Predictive Performance of CCI and ECS

Comparison of the prognostic value of Charlson and Elixhauser comorbidity measures in ACS patients: a national registry database study

7.1 INTRODUCTION

This chapter addresses the third objective set in section 1.2 of the thesis by comparing the performance of two widely accepted comorbidity measures in predicting ACS outcomes. The findings from this chapter were published in the Journal of Clinical Epidemiology.

In previous chapters, two broadly validated comorbidity measures were used to consider the global comorbidity burden in ACS patients rather than only applying individual comorbidities. Their results have demonstrated that the total comorbidity burden of ACS patients has been increasing over years, and the severe comorbid burden that was defined by either CCI or ECS was both associated with worse adverse outcomes and less rate of utilisation of invasive treatments. It can be seen that the comorbidity burden may impact the rehabilitation potential of ACS patients and the choice of the treatment strategy in practice [57, 58, 109]. Thus, ESC recommends that comorbidity burden should be considered in the decision-making processes in guiding the management of ACS patients. There is a growing interest in using measures of comorbidity burden to improve the prognosis in patients with ACS or adding comorbidity measures into prediction models of ACS outcomes for risk adjustment [103]. Nonetheless, it is still no widely accepted conclusion regardingwhich measure defines comorbidity better in ACS patients in practice. The CCI and ECS are well-validated measures of comorbid burden, and both have been broadly used for risk assessment in various populations. Chapter 3 found that whilst a small number of studies have compared the performance of the ECS and CCI in patients with ACS, with studies reporting that ECS might outperform CCI in the prediction of ACS outcomes [83, 97], these studies were limited for several reasons. Most of these studies were derived from patient

populations with small sample sizes or come from cohorts that were of historical interest. Many of these studies have used component comorbidities of the CCI and ECS as binary prognostic factors in the predictive models, prior to the development of the ECS scoring system which limited their applicability in contemporary practice, particularly when both scoring systems are well established and in widespread use. Hence, it is necessary to update this information using a larger dataset and explore which comorbidity measure's performance in the risk assessment of ACS outcomes is better based on their scoring systems.

7.2 SPECIFIC OBJECTIVES

The main objective of this analysis was to compare the prognostic value of the CCI and ECS in predicting clinical outcomes using their scoring systems. The specific objectives of this chapter were designed as follows:

I. To describe the statistics in the baseline characteristics, comorbidities, outcomes, procedures of ACS patients
II. To fit a series of models using two different comorbidity measures, respectively.
III. To calculate the C-statistics, AIC and BIC of each model and then compare their performance in predicting outcomes correspondingly.
IV. To visualize the results.

7.3 METHODS

7.3.1 Data Processing

Full details of the database used (NIS dataset) have already been described in chapter 4. The data and all variables needed in this chapter were already produced in chapters 5 and 6, no new data is needed in this chapter

except generating some new variables used in the sensitivity analysis in this chapter. Given the complexity of my dataset, a method in STATA 14.0 was not found to calculate the AIC and BIC on the survey data with weight application and multiple imputations. Therefore, from this chapter, apart from using STATA, I processed the dataset from the format for STATA 14.0 into the format that the R language can read.

7.3.2 Study Design and Outcomes

Baseline patient characteristics include age, gender, race, admission day (weekday or weekend), median household income for patient's ZIP code, Charlson comorbidities, Elixhauser comorbidities, other clinically relevant comorbidities (smoking, atrial fibrillation, long-term use of anticoagulants, previous PCI, previous CABG), and procedural characteristics such as PCI, CA, CABG, thrombolysis and IABP. Primary outcomes include in-hospital mortality, MACCE and major bleeding.

7.3.3 Charlson/Deyo and Elixhauser

In this analysis, the Deyo definition of the CCI was used, which included 17 comorbidities [74]. The ECS developed by Van Walraven et al. was utilised and included 30 comorbidities (29 in the thesis) [81]. The CCI and ECS were developed by assigning a weighting to each included comorbid condition based on its observed association with 1-year all-cause mortality. These weightings are then used to provide an overall score for each patient representing their comorbidity burden. Based on the cut-off methods in the CCI and ECS original paper, total CCI scores for each patient were categorised into four commonly used levels: "0" no comorbidity, "1" mild comorbid condition, "2" moderate condition, "≥3" severe comorbid burden; ECS scores were categorized into five commonly used levels that correspond to ECS<0, =0, 1-5, 6-13, ≥14.

7.3.4 Statistical Analysis

Description of the data is presented using the median and IQR for continuous variables and number and percentage for categorical variables. MICE was applied both in the dataset used in R language and the dataset for calculation of C-statistic in STATA, respectively, to impute missing data in age, sex, race, household income and mortality variables. Model parameters and performance statistics were estimated within imputation datasets. C-statistics were combined using Rubin's Rules [130]. AICs/BICs values were compared in two ways: 1) randomly chose one of the twenty imputed datasets and then compared the AICs/BICs values for each model of each outcome within this dataset, 2) compared AICs/BICs in pairs within the 20 imputed datasets for each model of each outcome. All variables included in the analysis model, potential confounders and outcomes were included in the imputation model to ensure congeniality between analysis and imputation models [131].

A series of multivariable logistic regression models were utilized to compare the relative contribution of the CCI and ECS to the prediction of in-hospital adverse outcomes including mortality, major bleeding and MACCE, after adjusting for variables with known clinical importance and potential confounders. Seven logistic regression models were fitted for each of the outcomes, resulting in a total of 21 models: 1) the basic model only included patient demographic information, which provided a baseline measurement for evaluating the relative contribution of controlling for comorbidities; 2) based on the basic model, the second model entered a block of other specific risk factors; 3) in the third model, procedural variables were added; 4-7) based on the third model, the CCI and ECS scores were added independently. Both the CCI and ECS were treated as categorical variables (as commonly used in practice and proposed by the original authors), and as continuous variables assuming

linearity. For example, the following seven models were compared for the outcome in-hospital mortality:

- Model 1: Age, gender, race, median income, day of admission, year
- Model 2: Model 1 + type of ACS, smoking, atrial fibrillation, long-term use of anticoagulants, prior PCI, prior CABG.
- Model 3: Model 2 + PCI, CA, thrombolysis, CABG, IABP.
- Model 4: Model 3 + categorical CCI.
- Model 5: Model 3 + continuous CCI.
- Model 6: Model 3 + categorical ECS.
- Model 7: Model 3 + continuous ECS.

I also examined simple non-linear forms of the continuous ECS and continuous CCI as a sensitivity analysis, which included:

- Model 8: Model 5 + continuous CCI^2.
- Model 9: Model 5 + continuous CCI^2 + continuous CCI^3.
- Model 10: Model 7 + continuous ECS^2
- Model 11: Model 7 + continuous ECS^2 + continuous ECS^3

To evaluate the prognostic value of the comorbidity measures, for each of the eleven models, for all outcomes, I calculated the C-statistic [152], AIC [153, 154] and BIC [154, 155]. The pooled C-statistic for each model-outcome combination from the imputed datasets were calculated. Given the dataset was extremely large (>7 million records), I refrained from testing for a difference in C-statistics, as any p-value would be an unreliable indicator. Hence, point estimates and 95% CI for each C-statistic using the bootstrap procedure were examined to compare model discrimination. It was broadly considered 95%CIs that crossed each other to indicate that there was not a statistically significant difference between the discrimination of the models being compared, but

emphasize the width of the interval [156, 157]. AIC and BIC provide a means to assess a model's goodness of fit, while penalising models with greater complexity [153, 155]. The AIC and BIC can be compared as a difference relative to the lowest value, among models having the same dependent variable but with different numbers of independent variables. Unlike the likelihood ratio test, comparing AIC or BIC does not require models be nested [158, 159]. Models with the lowest AIC or BIC were preferred. A difference in AIC or BIC between models of < 2, 4-7, and >10 was interpreted as no, weak, and strong evidence of improved model fit, respectively [160].

All analyses regardless of the R language or STATA were conducted using survey estimation commands to obtain a national estimate, which is the recommendation from AHRQ. Model analyses to calculate C-statistics were performed using STATA version 14.0, analyses using AIC and BIC were performed using "survey" packages [161] using R language version 3.6.2.

7.4 RESULTS

From 2004 to 2014, a total of 7,201,900 weighted records ≥18 years of age with a principal diagnosis with ACS were included in the analysis, with at most 18% missing data in a single variable. Descriptive statistics of baseline characteristics, treatments, outcomes, and comorbidities before multiple imputations are listed in **Table 7.1**. 33.1% of patients had a STEMI, the median age of the whole dataset was 67 (56-79) years old, women accounted for 40.3% of the population. The prevalence of diabetes was 33.9%, with 10.2% of the population with a previous history of MI. 62% of the population received CA and 40.7% of the population received revascularisation with PCI.

Table 7.1: Summary statistics of ACS patient baseline characteristics before multiple imputations of missing data.

Patient demographics	**Summary (% of n=7,201,900)**	**Missing data (% of n=7,201,900)**
No. of STEMI	2,380,808 (33.1%)	NA
Median (IQR) age, y	67(56, 79)	0.009%
Patient demographics	**Summary (% of n=7,201,900)**	**Missing data (% of n=7,201,900)**
Female	40.3%	0.014%
Admission/weekend	25.8%	NA
Race		
White	76.3%	17.4%
Black	10.0%	
Hispanic	7.6%	
Asian/Pacific islander	2.2%	
Native American	0.6%	
Other	3.2%	
Median income		
Frist	29.0%	2.4%
Second	27.3%	
Third	23.5%	
Fourth	20.1%	
Treatments		
PCI	40.7%	NA
CA	62.0%	NA
Thrombolysis	1.3%	NA
CABG	8.4%	NA
IABP	4.6%	NA
Outcomes		
Death	5.5%	0.04%
Major Bleeding	4.8%	NA
MACCE	8.0%	NA
Comorbidities	**Summary (% of n=7,201,900)**	**Comorbidity index in which included**
Previous Myocardial infarction	10.2%	CCI
Previous Cerebrovascular disease	1.5%	CCI
Dementia	0.7%	CCI

Comorbidities	Summary (% of n=7,201,900)	Comorbidity index in which included
Mild liver disease	0.5%	CCI
Moderate or severe liver disease	0.2%	CCI
Congestive heart failure	0.8%	CCI and ECS
Peripheral vascular disease	10.5%	CCI and ECS
Chronic pulmonary disease	20.5%	CCI and ECS
Rheumatologic/collagen vascular disease	2.1%	CCI and ECS
Peptic ulcer	0.03%	CCI and ECS
Diabetes, uncomplicated	28.0%	CCI and ECS
Diabetes with chronic complications	5.9%	CCI and ECS
Paralysis/hemiplegia	1.6%	CCI and ECS
Moderate/severe renal disease		CCI
Renal Disease	15.8%	ECS
Any malignancy including leukaemia and lymphoma	0.5%	CCI and ECS
Metastatic cancer	0.8%	CCI and ECS
AIDS	0.1%	CCI and ECS
Solid tumour without metastasis	1.4%	ECS
Liver disease	1.2%	ECS
Hypertension	66.4%	ECS
Depression	6.4%	ECS
Valvular disease	0.2%	ECS
Pulmonary circulation disorders	0.1%	ECS
Neurodegenerative disorders	5.7%	ECS
Hypothyroidism	9.6%	ECS
Coagulopathy	4.1%	ECS
Obesity	11.7%	ECS
Weight loss	2.0%	ECS
Fluid and electrolyte disorders	18.5%	ECS
Blood loss anemia	1.0%	ECS
Deficiency anemia	14.2%	ECS
Alcohol abuse	2.8%	ECS
Drug abuse	2.0%	ECS
Psychosis	2.1%	ECS
Other conditions		
Smoking	33.8%	
Atrial Fibrillation	16.6%	

Long-term use of anticoagulants	2.9%
Previous PCI	11.3%
Previous CABG	7.5%

ACS: acute coronary syndrome; STEMI: ST-elevation myocardial infarction; IQR: interquartile range; PCI: percutaneous coronary intervention; CA: coronary angiography; CABG: coronary artery bypass graft; IABP: intra-aortic balloon pump; MACCE: major acute cardiovascular and cerebrovascular events: composite of death, cardiac complications, stroke, and vascular complications.

Table 7.2 presents the C-statistics from the seven different logistic regression models predicting the risk of each of the in-hospital outcomes of interest; mortality, MACCE and major bleeding. For every outcome, compared to the baseline models, adding risk factors, interventions or comorbidity measures consistently improved the model's performance as evidenced by an increase in C-statistic. For example, when predicting mortality, the C-statistic of the model including interventions (Model 3) was 0.818 (95% CI: 0.817, 0.819), which was substantially higher than the baseline model (Model 1: 0.692 (95% CI: 0.690, 0.693)) and the model with risk factors added (Model 2: 0.752 (95% CI: 0.750, 0.753)). For all outcomes in this study, models using the ECS as a measure of comorbidity, showed higher C-statistics compared to models using the CCI, irrespective of whether the score was defined as a categorical or continuous variable. Models with the highest discrimination for mortality and MACCE were those incorporating the ECS as a continuous score (Model 7: 0.837 (95% CI: 0.836, 0.839) and 0.776 (95% CI: 0.774, 0.777), respectively), and as a categorical score (Model 6: 0.837 (95% CI: 0.836, 0.838) and 0.775 (95% CI: 0.773, 0.776), respectively). However, differences in discrimination between model 6 (where ECS was used as a categorical score) and model 7 (where ECS was used as a continuous score) for in hospital mortality and MACCE were not significantly different **(Figure 7.1)**. It was observed that the best model for the prediction of bleeding was using ECS as a categorical score (Model 6: 0.668 (95% CI: 0.666, 0.670)), closely followed by the model using ECS as a continuous score (Model 7: 0.659 (95% CI: 0.657, 0.661)).

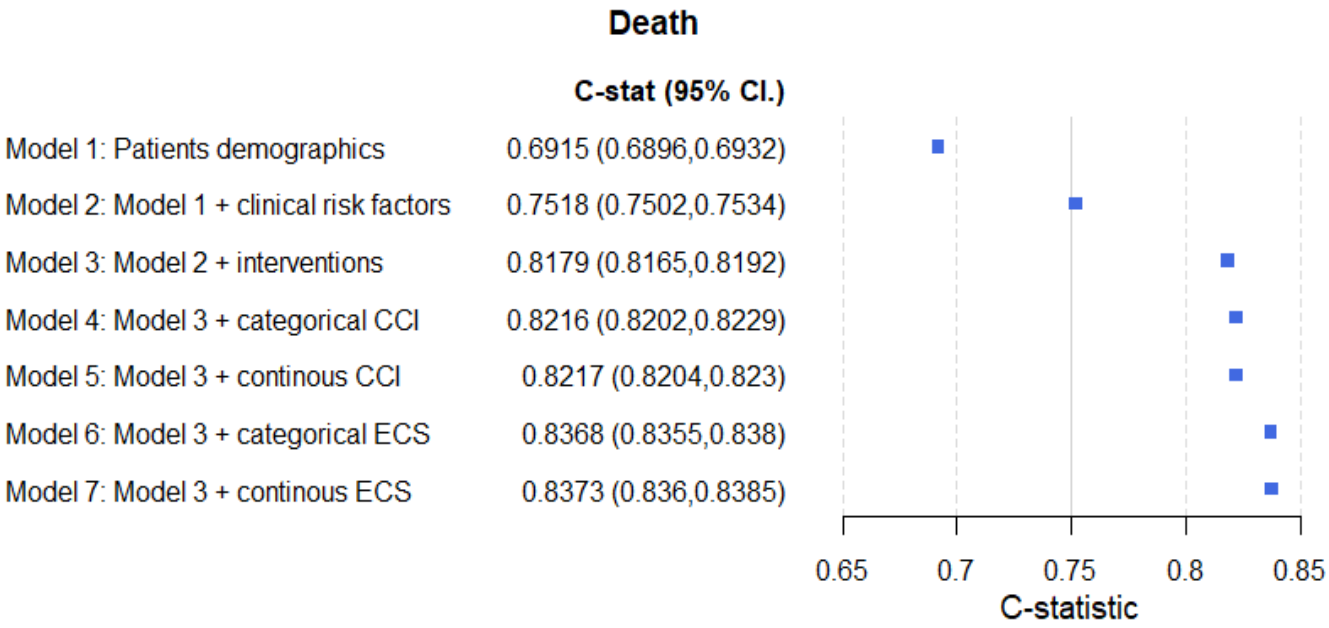
Table 7.2: C-statistics with 95% confident internal (CI) from logistic regression models in predicting in-hospital outcomes.

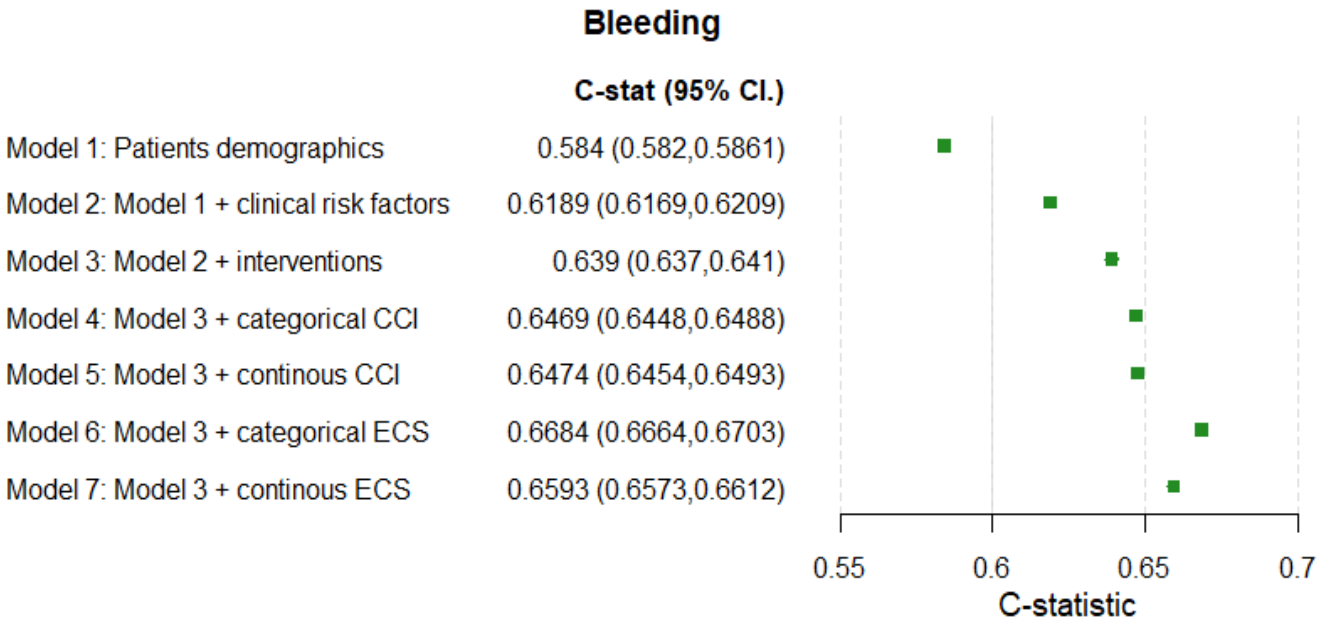
Models*	Different adverse Outcomes					
	Death		Bleeding		MACCE	
	C-statistic	95% CI	C-statistic	95% CI	C-statistic	95% CI
Model 1: Patient's demographics.	0.6915	(0.6896, 0.6932)	0.5840	(0.5820, 0.5861)	0.6497	(0.6481, 0.6513)
Model 2: Model 1 + clinical risk factors.	0.7518	(0.7502, 0.7534)	0.6189	(0.6169, 0.6209)	0.7053	(0.7038, 0.7067)
Model 3: Model 2 + interventions.	0.8179	(0.8165, 0.8192)	0.6390	(0.6370, 0.6410)	0.7503	(0.7489, 0.7517)
Model 4: Model 3 + categorical CCI.	0.8216	(0.8202, 0.8229)	0.6469	(0.6448, 0.6488)	0.7551	(0.7537, 0.7565)
Model 5: Model 3 + continuous CCI.	0.8217	(0.8204, 0.8230)	0.6474	(0.6454, 0.6493)	0.7554	(0.7539, 0.7568)
Model 6: Model 3 + categorical ECS.	0.8368	(0.8355, 0.8380)	0.6684	(0.6664, 0.6703)	0.7748	(0.7734, 0.7761)
Model 7: Model 3 + continuous ECS.	0.8373	(0.8360, 0.8385)	0.6593	(0.6573, 0.6612)	0.7755	(0.7741, 0.7769)

ECS: Elixhauser comorbidity score; CCI: Charlson comorbidity index; MACCE: major acute cardiovascular and cerebrovascular events: composite of death, cardiac complications, stroke, and vascular complications.

*95% CIs that crossed each other indicated there was not a statistically significant difference between the discrimination of the models being compared.

Figure 7.1: Forest plots for the C-statistics with 95%CI from logistic regression models in predicting in-hospital outcomes.




Bleeding
C-stat (95% CI.)
Model 1: Patients demographics
0.584 (0.582,0.5861)
Model 2: Model 1 + clinical risk factors
0.6189 (0.6169,0.6209)
Model 3: Model 2 + interventions
0.639 (0.637,0.641)
Model 4: Model 3 + categorical CCI
0.6469 (0.6448,0.6488)
Model 5: Model 3 + continous CCI
0.6474 (0.6454,0.6493)
Model 6: Model 3 + categorical ECS
0.6684 (0.6664,0.6703)
Model 7: Model 3 + continous ECS
0.6593 (0.6573,0.6612)
0.55
0.6
0.65
0.7
C-statistic

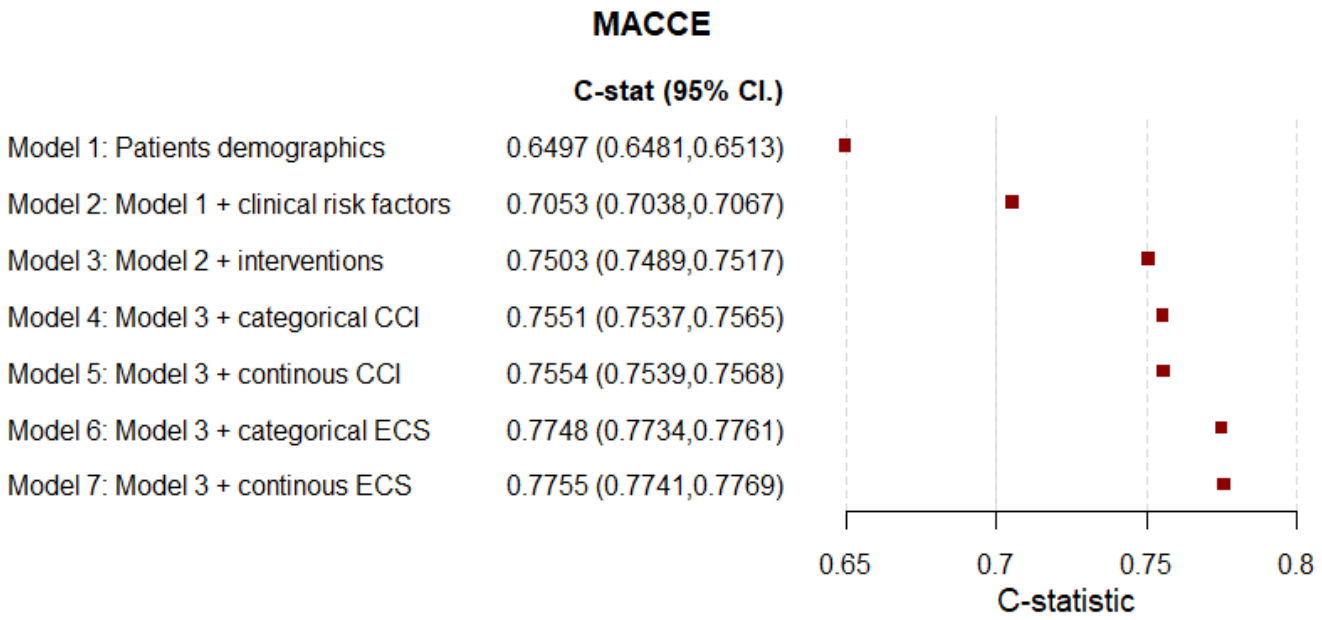

MACCE
C-stat (95% CI.)
Model 1: Patients demographics
0.6497 (0.6481,0.6513)
Model 2: Model 1 + clinical risk factors
0.7053 (0.7038,0.7067)
Model 3: Model 2 + interventions
0.7503 (0.7489,0.7517)
Model 4: Model 3 + categorical CCI
0.7551 (0.7537,0.7565)
Model 5: Model 3 + continous CCI
0.7554 (0.7539,0.7568)
Model 6: Model 3 + categorical ECS
0.7748 (0.7734,0.7761)
Model 7: Model 3 + continous ECS
0.7755 (0.7741,0.7769)
0.65
0.7
0.75
0.8
C-statistic

Table 7.3 and **Figure 7.2** provide an overview of AIC and BIC values for model goodness-of-fit following the first comparison way. The results of the second comparison way were listed in **Appendix Table 7.1**. Similar to the C-statistics results, model goodness-of-fit was incrementally improved by adding risk factors, interventions, and comorbidities into the baseline model. For all outcomes studied, AIC or BIC values of models using ECS as a measure of comorbidity were much lower than (difference >10) those of models using CCI as a measure of comorbidity, which implies ECS consistently outperformed CCI on model goodness-of-fit. Continuous ECS score resulted in superior model fit to categorical ECS for mortality and MACCE but not for bleeding (where ECS categorical was superior): findings which were again consistent with the pattern of C-statistic results.

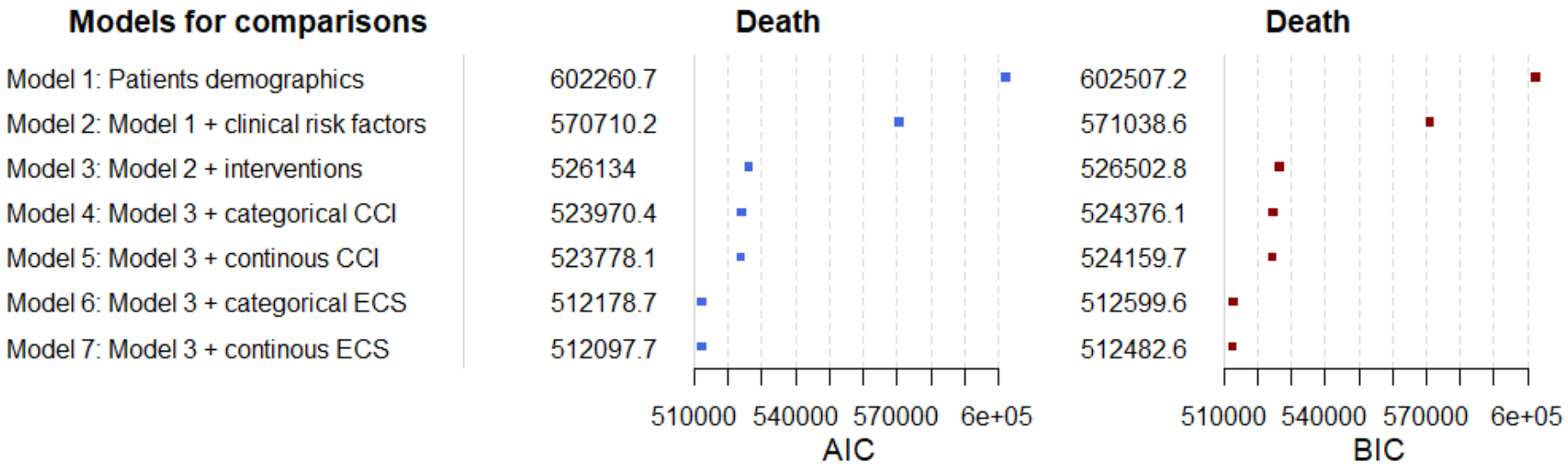
The linearity assumption for the continuous CCI model or continuous ECS model was explored in the sensitivity analysis. Adding non-linear terms of ECS or CCI into the model of in-hospital mortality did not improve the model discrimination (95%CI of C-statistics crossed) while this improved the discriminated ability of the model of in-hospital bleeding. For all outcomes, there were improvements in model goodness of fit when included non-linear terms into models with continuous CCI or continuous ECS. In addition, ORs of almost all non-linear terms were close to 1 or their 95%CI included 1 (e.g., ECS^3 for mortality: OR:1.00001 95%CI: 0.99999-1.00003). Detailed results were provided in **Appendix Table 7.2**. As another sensitivity analysis, I also re-ran models without the inclusion of interventions such as cardiac catheterisation or receipt of PCI, and the findings remained consistent, in that the Elixhauser score outperformed the Charlson score (**Appendix Table 7.3**).

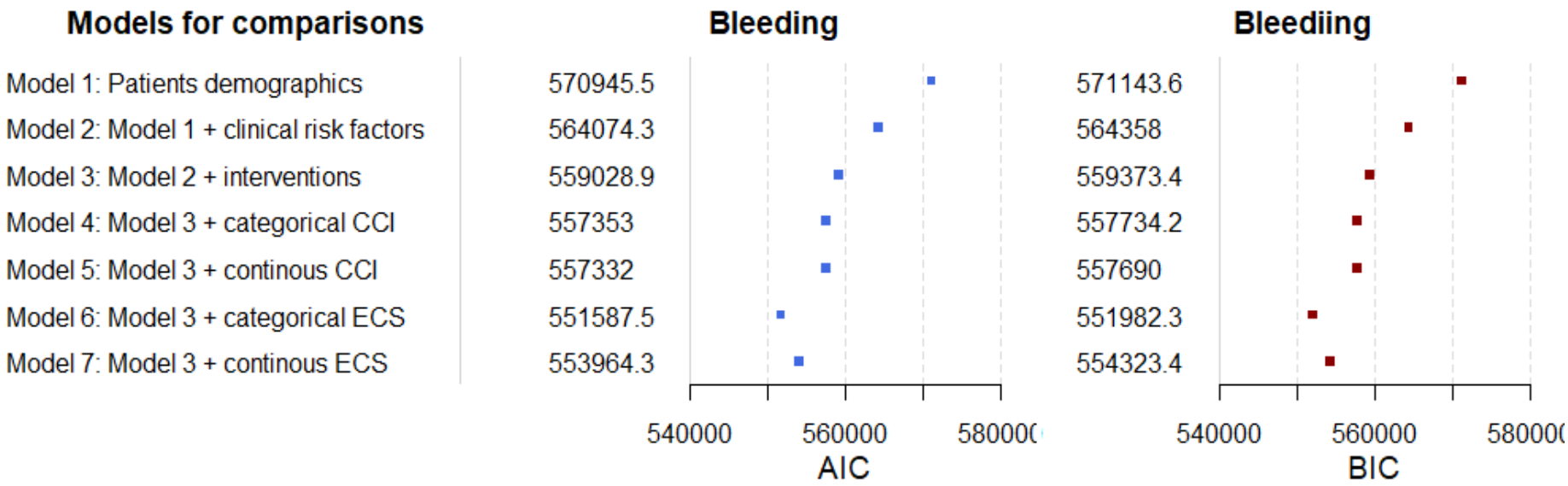
Table 7.3: AIC and BIC for Model goodness-of-fit from logistic regression models in predicting in-hospital outcomes (following the first comparison way).

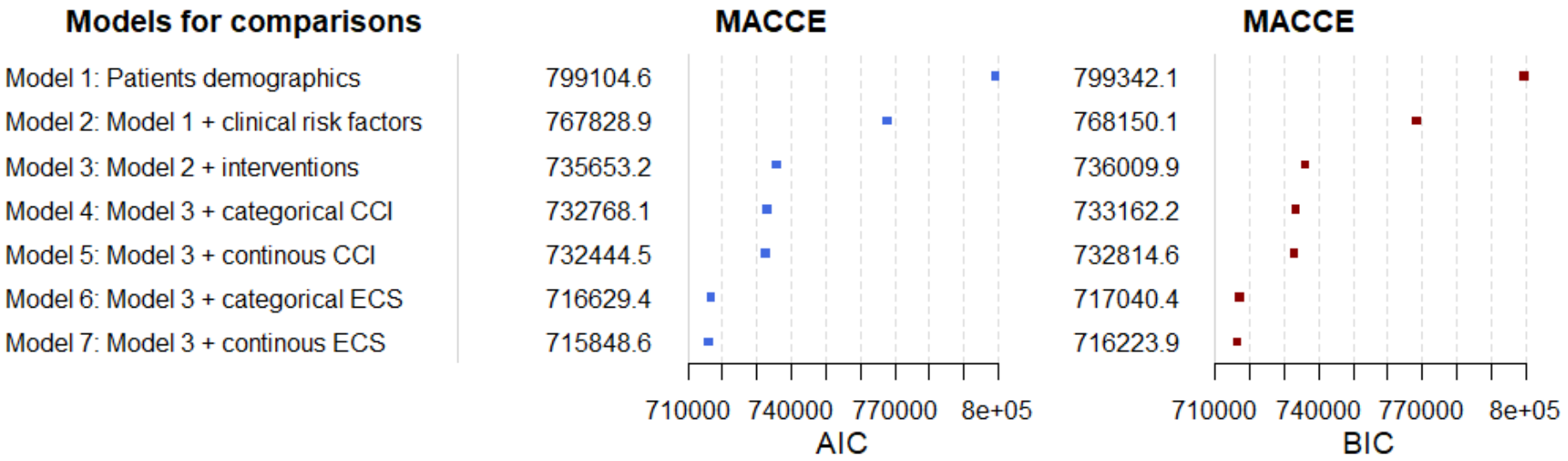
Models*	Different adverse Outcomes					
	Death		Bleeding		MACCE	
	AIC	BIC	AIC	BIC	AIC	BIC
Model 1: Patient's demographics.	602260.7	602507.2	570945.5	571143.6	799104.6	799342.1
Model 2: Model 1 + clinical risk factors.	570710.2	571038.6	564074.3	564358.0	767828.9	768150.1
Model 3: Model 2 + interventions.	526134.0	526502.8	559028.9	559373.4	735653.2	736009.9
Model 4: Model 3 + categorical CCI.	523970.4	524376.1	557353.0	557734.2	732768.1	733162.2
Model 5: Model 3 + continuous CCI.	523778.1	524159.7	557332.0	557690.0	732444.5	732814.6
Model 6: Model 3 + categorical ECS.	512178.7	512599.6	551587.5	551982.3	716629.4	717040.4
Model 7: Model 3 + continuous ECS.	512097.7	512482.6	553964.3	554323.4	715848.6	716223.9

ECS: Elixhauser comorbidity score; CCI: Charlson comorbidity index; MACCE: major acute cardiovascular and cerebrovascular events: composite of death, cardiac complications, stroke, and vascular complications.
*A difference in AIC or BIC between models of < 2, 4-7, and >10 was interpreted as no, weak, and strong evidence of improved model fit, respectively.

Figure 7.2: Plots for the AIC and BIC for Model goodness-of-fit from logistic regression models in predicting in-hospital outcomes.




Models for comparisons
Model 1: Patients demographics
Model 2: Model 1 + clinical risk factors
Model 3: Model 2 + interventions
Model 4: Model 3 + categorical CCI
Model 5: Model 3 + continous CCI
Model 6: Model 3 + categorical ECS
Model 7: Model 3 + continous ECS
Bleeding
570945.5
564074.3
559028.9
557353
557332
551587.5
553964.3
540000
560000
AIC
Bleediing
571143.6
564358
559373.4
557734.2
557690
551982.3
554323.4
540000
560000
BIC



AIC: Akaike information criterion; BIC: Bayesian information criterion. ECS: Elixhauser comorbidity score; CCI: Charlson comorbidity index; MACCE: major acute cardiovascular and cerebrovascular events: composite of death, cardiac complications, stroke, and vascular complications.

7.5 DISCUSSION

This study extends and updates previous comparative studies of the predictive performance of Charlson and Elixhauser comorbidities indexes, by applying both methods' scoring systems to a nationwide database of hospitalisation of ACS patients with multiple adverse outcomes from 2004-2014. The findings suggest that the ECS method significantly outperforms the CCI method in predicting important in-hospital adverse outcomes studied in terms of model discrimination and goodness of fit, irrespective of whether the comorbidity measures were defined as categorical or continuous variables. In summary from two different performance measures, models using the ECS measure as a continuous variable might provide better goodness of fit (and hence risk adjustment) although the improvement in model discrimination over the models using it as a categorised score is minor and, for predicting bleeding, may even be inferior.

There are several studies that have been conducted to compare the predictive performance of the CCI and ECS measures [82, 83, 99], which support my findings, albeit in different clinical settings. A study using data between 2008-2009 from five European countries indicated that the ECS had better performance than the CCI in predicting 30-day mortality in acute MI patients [82]. Southern et al. also reported that models based on the ECS method discriminated better than the CCI using Canadian administrative data on 4,833 patients with MI [99]. However, all the studies that included ECS measure applied its comorbidities as separate binary variables in the model rather than using its scoring system due to the lack of the weighting algorithm of the original ECS method at that time. Nevertheless, even though the CCI score is widely used in clinical practice, previous studies still used Charlson comorbidities as

individual binary variables instead of using Charlson weights to compare with ECS. It is possible that modelling the ECS and CCI in this way could lead to the models using Elixhauser comorbidities having a higher C-statistic or being overfitted compared to the ones using Charlson comorbidities as Elixhauser contains nearly twice the number of conditions [114], potentially leading to bias. My study utilised both the Charlson and Elixhauser's weighting systems for a direct comparison of their predictive performance across three important in-hospital outcomes. In addition, this analysis included over 7 million ACS admissions that gives this analysis the statistical power to detect even small differences in comparative performance.

The findings on in-hospital mortality contribute further evidence to the findings of three earlier studies [82, 83, 99] that also demonstrated that the ECS more optimally predicted in-hospital mortality compared to the CCI score. For example, Stukenborg et al. found ECS outperformed CCI in predicting in-hospital mortality in 5 clinical categories of California hospital patients from 1994 to 1997 (acute MI, congestive heart failure, chronic obstructive pulmonary disease, hypertension with complications, and acute cerebrovascular disease) [99]. In addition, this study not only investigated in-hospital mortality but also included other adverse outcomes such as in-hospital MACCE and bleeding, which built upon prior comparative studies of ECS and CCI that only considered mortality, and might contribute to a greater general understanding of the performance of comorbidity measures, particularly when considering outcomes other than mortality. It reports that the ECS displayed better performance than the CCI score for all adverse outcomes studied irrespective of whether the comorbidity score was treated as a categorical or continuous variable in the model. Not only that, but the results also showed models using the ECS as a continuous variable were a little better in terms of model goodness of fit, than

ones using it as a categorical variable, when predicting mortality and MACCE. This observation may be due to underestimation of variation caused by categorising a continuous variable. When categorising a continuous variable at several cut points, it is treating individuals either side of a cut-point as distinctly different, when they may in fact be very similar, and individuals within a group as similar, when there may in fact be large variation in outcome risks within the group [162].

ESC clinical practice guidelines in patients with ACS suggests clinicians should take comorbidity into account for risk-adjustment in predicting patient prognosis or developing treatment strategies as comorbidity can have a substantial impact on patient outcomes and decision-making of the intervention [111]. However, there is so far no explicit definition in what comorbidity indices should be used to measure the comorbid burden in ACS patients. My study reports that risk-adjustment models using the ECS to define comorbid burden had better performance in predicting in-hospital outcomes than the ones using CCI. Clinicians are advised to focus efforts in using ECS to define the comorbid burden and consider integrating ECS into the existing ACS prognosis scores such as the GRACE risk prediction index [163].

7.6 LIMITATIONS

This study has some limitations. Similar to Chapters 5 and 6, the NIS dataset has potential selection bias due to coding errors. Furthermore, this analysis was limited to clinical outcomes during the hospital stay because data for post-discharge outcomes are not captured in the NIS database, which limits the ability to conduct comparisons of comorbidity measures when investigating longer-term outcomes. Nevertheless, these findings are still clinically relevant, particularly when related to in-hospital outcomes, for example when risk

adjusting and benchmarking of in-hospital clinical outcomes. However, I cannot speculate whether ECS still outperforms CCI in long-term ACS outcomes. However, a previous study [97] reported that the performance of ECS was better than CCI in predicting long-term (1-year) mortality in patients with acute MI, which was consistent with my findings in the in-hospital outcomes. Even so, this previous study still had the limitations highlighted previously (did not use scores), therefore, these findings should drive further research into the performance of ECS and CCI relating to post discharge outcomes. Moreover, it was found that the performance of the Elixhauser score in a continuous form was better than the performance of it in a categorical form for in-hospital mortality and MACCE. However, this conclusion is based on assuming that the continuous form of the ECS (and CCI) variable has a linear relationship with the outcome [164]. It was explored this assumption by adding simple non-linear terms (i.e., ECS/CCI score squared and cubed) to the models that used the ECS/CCI as a continuous score. Although the model fit was improved when including non-linear terms, the size of the effects (ORs) of the non-linear terms was extremely close to 1 or at least half of their 95%CIs crossed 1, which implied no strong evidence of a non-linear relationship between the continuous form of ECS/CCI and clinical outcomes. Given the complexity of my analyses, which included using multiple imputation and survey weightings, it was unable to explore more complex non-linear functions such a fractional polynomials or splines due to computational limitations. Further research may look to explore more complex non-linear relationships between patient outcomes and comorbidity measures such as the ECI and CCI in simpler examples.

7.7 CONCLUSION

In conclusion, based on analyses of nationally representative US data

from 2004-2014, the Elixhauser measure outperforms the Charlson method in predicting several important in-hospital outcomes and should therefore be preferred for risk adjustment in future work to investigate whether their performance improves and whether they optimise patient centred approaches in ACS management.

Chapter 8 -
Agreement Between CCI and ECS in Classifying Patients

Agreement analysis between Charlson and Elixhauser Comorbidity Index Scores in Patients with Acute Coronary Syndrome

8.1 INTRODUCTION

In line with section 1.2 of the thesis, this chapter was aimed to address the fourth objective by researching how the two common comorbidity measures overlap between each other and the degree of agreement between them. The manuscript from this chapter is currently under review in peer review in the Heart Lung and Circulation.

Increases in life expectancy and advances in healthcare provision have increased the size of the elderly population living with comorbidities, who constitute a significant proportion of patients presenting with an ACS [53, 165]. In addition, Comorbidities occur seldom in isolation, with patients presenting with ACS often burdened with multiple comorbid conditions [109, 166], therefore patients' comorbidity burden should be considered and assessed in totality. The CCI and the ECS are two well-validated measures to define the overall comorbidity burden, and both have been broadly used for risk assessment in prognosis for both CV and non-CV conditions [72-74, 78, 81, 167, 168]. Previous chapters have used these two measures in the investigation of ACS prognosis and demonstrated that a greater comorbidity burden defined by either CCI or ECS is associated with worse clinical outcomes (such as death and major bleeding) and less receipt of invasive treatments including PCI and CABG; I also compared their predictive performance in ACS patients and reported that ECS might have better prognosis value than the CCI. However, there has been no study investigating whether the two measures that are used to define patients with significant comorbidities identify the same groups of patients as being comorbid on the same level or whether they identify different groups of patients within a population. Furthermore, there is no data around the level of agreement between the two measures of comorbidity burden. This is

important particularly when clinical guidelines suggest that comorbidity burden should be considered when managing patients with ACS, and so it is important to study whether the two most commonly used measures of comorbidity burden agree with each other, that is to say, it would make management of patients challenging if they were considered comorbid by one score but not the other. Understanding the degree of overlap/agreement of these scores is critical for clinicians, as highlighted by my principal supervisor (Professor Mamas Mamas) for future ESC 2023 ACS guidelines for which he is a reviewer. This study, therefore, aimed to provide a comprehensive examination around the overlap in the populations identified as having different burdens of comorbidity by CCI and ECS measures, as well as studying the relationship between different combinations of CCI and ECS comorbidity burden on the utilisation of invasive therapies and clinical outcomes in a national cohort of patients with ACS in the US.

8.2 SPECIFIC OBJECTIVES

In order to achieve the above goal, the specific objectives of this chapter were designed as follows:

I. To describe the statistics of the characteristic of the baseline variables, comorbidities, use of treatments and clinical outcomes in the whole ACS dataset.

II. To stratify total ECS and CCI scores into the same numbers of groups based on clinicians' consensus; calculate the proportions of weighted patients whose comorbidity burden stratification agreed between ECS and CCI groups, and calculate the kappa value.

III. To calculate the proportion of weighted patients over the whole population in each subgroup created by the agreement analysis;

summary the proportion of weighted patients undergoing procedures or encountering adverse outcomes in each subgroup.

IV. To explore whether there is a difference in the management strategy offered to patients based on these subgroups, and the association of these subgroups with ACS outcomes.

V. To conduct the data visualisation and tabulation for each goal.

8.3 METHODS

8.3.1 Data Processing

Full details of the database that was used (NIS dataset) have already been described in chapter 4. However, this chapter needs to test the degree of agreement between the two measures, which requires targeted processing of the original dataset. A brief summary of this data processing is provided here. First, all comorbidities in the two measures need to be processed to ensure the subsequent analysis. The shared comorbidities in the two measures were combined based on the ECS measure because the ECS was already contained in the NIS database which could reduce the bias caused by ICD-9-CM codes. This process was double-checked by clinicians to ensure the feasibility of the mergence. Then, CCI scores were stratified into four categories in the original paper while ECS scores were five groups. I re-stratified the ECS scores into four groups by merging the first two ECS categories (ECS<0 and ECS=0). Finally, all analyse except for multivariable models were conducted in R language, I formatted the dataset from STATA 14 to R format.

8.3.2 Study Design and Outcomes

From 2004 to 2014, all individuals ≥18 years with a principal diagnosis of ACS were eligible for inclusion.

Baseline characteristics include patient demographics, procedural variables such as CA and PCI, 29 Elixhauser comorbidities described by Van Walraven et al., and 17 Charlson comorbidities modified by Deyo. Since the NIS database has already included Elixhauser comorbidities, diagnosis codes or procedure codes in NIS were used to identify Charlson comorbidities that are not included in Elixhauser. A list of ICD-9-CM codes used to extract those diseases is provided in previous chapters. Each condition in both Elixhauser and Charlson was weighted into a single numeric score based on their association with in-hospital mortality in the original cohort by Van Walraven et al and Deyo, respectively. These scores can be calculated into an overall score for each patient to represent their comorbidity burden. The main clinical outcomes were in-hospital mortality, MACCE, major bleeding, PCI and CA.

8.3.3 Statistical Analysis

All analyses in this report were performed on weighted data based on its sampling strategies in the NIS database to develop national estimates. Patient-level comorbidity severity agreement between ECS and CCI was investigated using data calculation, visualisation and tabulation.

It was decided, a priori, to stratify total ECS scores into 4 groups for the purpose of analysis: ≤0 (lowest ECS comorbid burden), 1-5 (mild), 6-13 (moderate), ≥14 (severe) [81] according to the severity of comorbid burden and categorise total CCI into 4 groups according to previous studies [74]: 0 (lowest CCI comorbid burden), 1 (mild), 2 (moderate), ≥3 (severe). Then, the proportions of weighted patients for whom comorbidity burden classification agreed between ECS and CCI groups were calculated using R language and the results were plotted into a mosaic diagram based on these proportions to show the situation of identifying patients by both CCI and ECS in the same population. Meanwhile,

Cohen's kappa (Cohen's κ) [169-171] was calculated to obtain the degree of their agreement. Cohen's κ is a statistic that is used to measure inter-rater reliability for categorical items [169]. In a broad sense, a kappa of <0.2 indicates a poor agreement and a kappa above 0.8 indicates very good agreement beyond chance [172].

Descriptive statistic was conducted to obtain the characteristic of the baseline variables, comorbidities, use of treatments and clinical outcomes based on those subgroups identified from the agreement analysis. Continuous variables are expressed as median with their corresponding interquartile range while categorical variables are presented as percentages. Next, bar charts were used to show the proportion of each subgroup created by the agreement analysis over the whole weighted population. In addition, contingency tables were used to summarise the proportions of patients undergoing procedures or encountering adverse outcomes in each subgroup. Moreover, ECS and CCI were merged into 32 comorbidities following medical advice from clinicians in order to obtain the proportion of each comorbidity in each subgroup, then was plotted into a heat-map with lattices for displaying and exploring. Colour differentiation of lattices was used to exhibit the levels of proportions.

Finally, MICE [128] were performed to impute the missing data in age, gender, race and death before running multivariable analysis. Logistic regression models were fitted using those imputed datasets where one of the ACS outcomes or the invasive treatments was the dependent variable, the ECS/CCI category combinations and three demographics (age, gender, ethnicity for adjustment) were predictors. The resulting OR estimates were combined using Rubin's Rules [130].

R version 3.6.2 and Stata 14.0 were used for statistical investigations. All analyses were based on the "survey" package [173] to achieve the weighting and

obtain the kappa value. Graphical plots were drawn using the packages "grid" [174], "lattice" [175] and "ggplot2" [176]. MICE and logistic models were based on Stata command "mi" and "svy".

8.4 RESULTS

A total of 7,201,900 weighted hospitalisations aged over 18 years old with a principal diagnosis of ACS between 2004 and 2014 in the NIS were included in this analysis with totally about 19.4% of missing data mainly found in race and less found in age, gender and death.

8.4.1 Patient Characteristics

Table 8.1 demonstrates the summary statistics for the baseline characteristics of the whole cohort. The median age of patients was 67 (56-79) years old and 40.3% were females. Hypertension (66.4%), uncomplicated diabetes (28.0%) and chronic pulmonary disease (20.5%) were the three most common comorbidities present in the population and 10.2% of patients had a prior history of myocardial infarction. The utilisation of CA was 62.0% and PCI was performed in 40.7% of the population. In-hospital death and MACCE occurred in 5.5% and 8.0% of the population respectively, whilst bleeding complications were encountered in 4.8% of patients. ECS≤0 category had the highest proportion of patients (52.2%), while the most severe comorbid group (ECS≥14) accounted for 3.5% of the total patients. CCI measure stratified 34.2% of total patients into "no comorbidity (CCI=0)" and 13.9% of patients into the most severe comorbidity group (CCI≥3).

Table 8.1: Summary statistics of baseline characteristics in ACS patient.

Patient demographics	**Summary (% of n=7,201,900)**	**Missing data (% of n=7,201,900)**
Median (IQR) age, y	67(56, 79)	0.009%
Female, %	40.3%	0.014%
Race, %		
White	74.1%	17.4%
Black	11.9%	
Hispanic	8.2%	
Asian/Pacific islander	2.6%	
Native American	0.7%	
Other	2.5%	
Treatments		
PCI	40.7%	NA
CA	62.0%	NA
Outcomes		
Death	5.5%	0.04%
Major Bleeding	4.8%	NA
MACCE	8.0%	NA

Comorbidities	**Summary (% of n=7,201,900)**	**Comorbidity index in which included**	**ECS score**	**CCI score**
Previous Myocardial infarction	10.2%	CCI		1
Previous Cerebrovascular disease	1.5%	CCI		1
Dementia	0.7%	CCI		1
Congestive heart failure	0.8%	CCI and ECS	7	1
Peripheral vascular disease	10.5%	CCI and ECS	2	1
Chronic pulmonary disease	20.5%	CCI and ECS	3	1
Rheumatologic/collagen vascular disease	2.1%	CCI and ECS	0	1
Peptic ulcer	0.03%	CCI and ECS	0	1
Diabetes, uncomplicated	28.0%	CCI and ECS	0	1
Diabetes with chronic complications	5.9%	CCI and ECS	0	2

Paralysis/hemiplegia	1.6%	CCI and ECS	7	2
Renal Disease	15.8%	CCI and ECS	5	2
Any malignancy including leukaemia and lymphoma	0.5%	CCI and ECS	9	2
Metastatic cancer	0.8%	CCI and ECS	12	6
AIDS	0.1%	CCI and ECS	0	6
Solid tumour without metastasis	1.4%	ECS	4	
Liver disease	1.2%	ECS	11	
Hypertension	66.4%	ECS	0	
Depression	6.4%	ECS	-3	
Valvular disease	0.2%	ECS	-1	
Pulmonary circulation disorders	0.1%	ECS	4	

Comorbidities	**Summary (% of n=7,201,900)**	**Comorbidity index in which included**	**ECS score**	**CCI score**
Neurodegenerative disorders	5.7%	ECS	6	
Hypothyroidism	9.6%	ECS	0	
Coagulopathy	4.1%	ECS	3	
Obesity	11.7%	ECS	-4	
Weight loss	2.0%	ECS	6	
Fluid and electrolyte disorders	18.5%	ECS	5	
Blood loss anemia	1.0%	ECS	-2	
Deficiency anemia	14.2%	ECS	-2	
Alcohol abuse	2.8%	ECS	0	
Drug abuse	2.0%	ECS	-7	
Psychosis	2.1%	ECS	0	

Charlson Comorbidity Index	**Summary (% of n=7,201,900)**
CCI = 0	34.2%
CCI = 1	32.3%
CCI = 2	19.5%
CCI ≥ 3	13.9%

Elixhauser Comorbidity Score	Summary (% of n=7,201,900)
ECS ≤ 0	52.2%
ECS = 1-5	27.3%
ECS = 6-13	17.0%
ECS ≥ 14	3.5%

ACS: acute coronary syndrome; IQR: interquartile range; PCI: percutaneous coronary intervention; CA: coronary angiography; MACCE: major acute cardiovascular and cerebrovascular events: composite of death, cardiac complications, stroke, and vascular complications; ECS: Elixhauser comorbidity score; CCI: Charlson comorbidity index.

8.4.2 Agreement

Figure 8.1 illustrates the mosaic plot for the agreement between CCI and ECS. When analysed, there were 16 combinations of ECS and CCI categories, with the size of the rectangles representing the size of the proportions of patients classified in each ECS/CCI subgroup. There seemed little agreement between severity as defined by CCI class and ECS class. For example, only half of patients (53.0%) classified as severe comorbidity burden by ECS (ECS≥14), were also severe as defined by Charlson (CCI≥3). Similarly, only half (50.8%) of patients defined as having low comorbidity with ECS (ECS≤0) had low comorbidity as defined by CCI (CCI=0). At the extremes, 4.2% of the subgroup with the lowest ECS (ECS≤0) had severe comorbid burden as defined by CCI (CCI≥3), whilst 5.5% of patients defined as severely comorbid by ECS (ECS≥14) were in the lowest comorbidity burden group as defined by CCI (CCI=0). The degree of agreement between CCI and ECS varied between 12.3% and 36.4% in the other combinations of comorbidity categories. Overall, the weighted Cohen's κ was 0.183 (95%CI: 0.181-0.184), which meant that the agreement between ECS and CCI was generally poor [169, 177].

The frequency-distribution of each combination of ECS/CCI category is presented in **Figure 8.2**. The "ECS≤0/CCI=0" subgroup had the highest proportion of patients (26.5%), whereas the subgroup of "ECS≥14/CCI≥3 which

contained the population that was defined as being severely comorbid by both measures of comorbidity accounted for 1.9% of the total patients. The demographic information of baseline characteristics, patients' comorbidities, treatment variables and clinical outcomes across the 16 combinations of ECS and CCI is provided in **Appendix Table 8.**

8.4.3 Management Strategy and Clinical Outcome

Table 8.2a and 8.2b describe the proportion of patients undergoing PCI or CA in each category of ECS and CCI combination, respectively. It can be seen that the proportion of patients receiving invasive management either in the form of CA or PCI decreased with increasing comorbidity burden amongst the 16 subgroups, with the lowest rates (36.2% and 17.3%) being observed in the ECS≥14/CCI≥3 cohort. **Tables 8.3a-c** present in hospital mortality, major bleeding and MACCE outcomes in the different categories of ECS and CCI combination. Generally, the lowest rates of adverse outcomes were encountered in the lowest comorbidity burden category (ECS≤0/CCI=0 group), with the rate of adverse outcomes increasing as the severity of comorbidity combinations increased, across all outcomes studied.

Figure 8.1: the mosaic plot for the agreement between the different CCI and ECS classes.

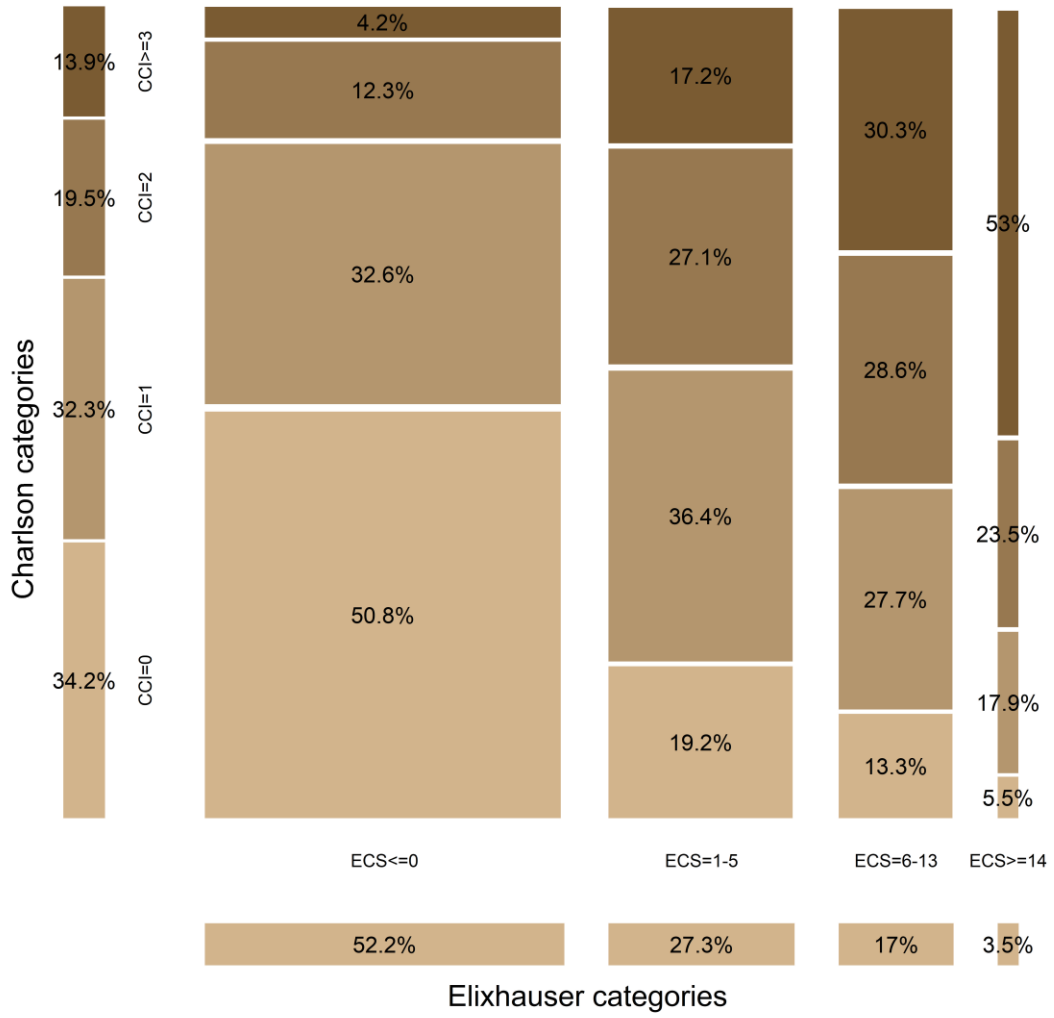


Figure 8.2: The frequency-distribution of each combination of ECS/CCI category.

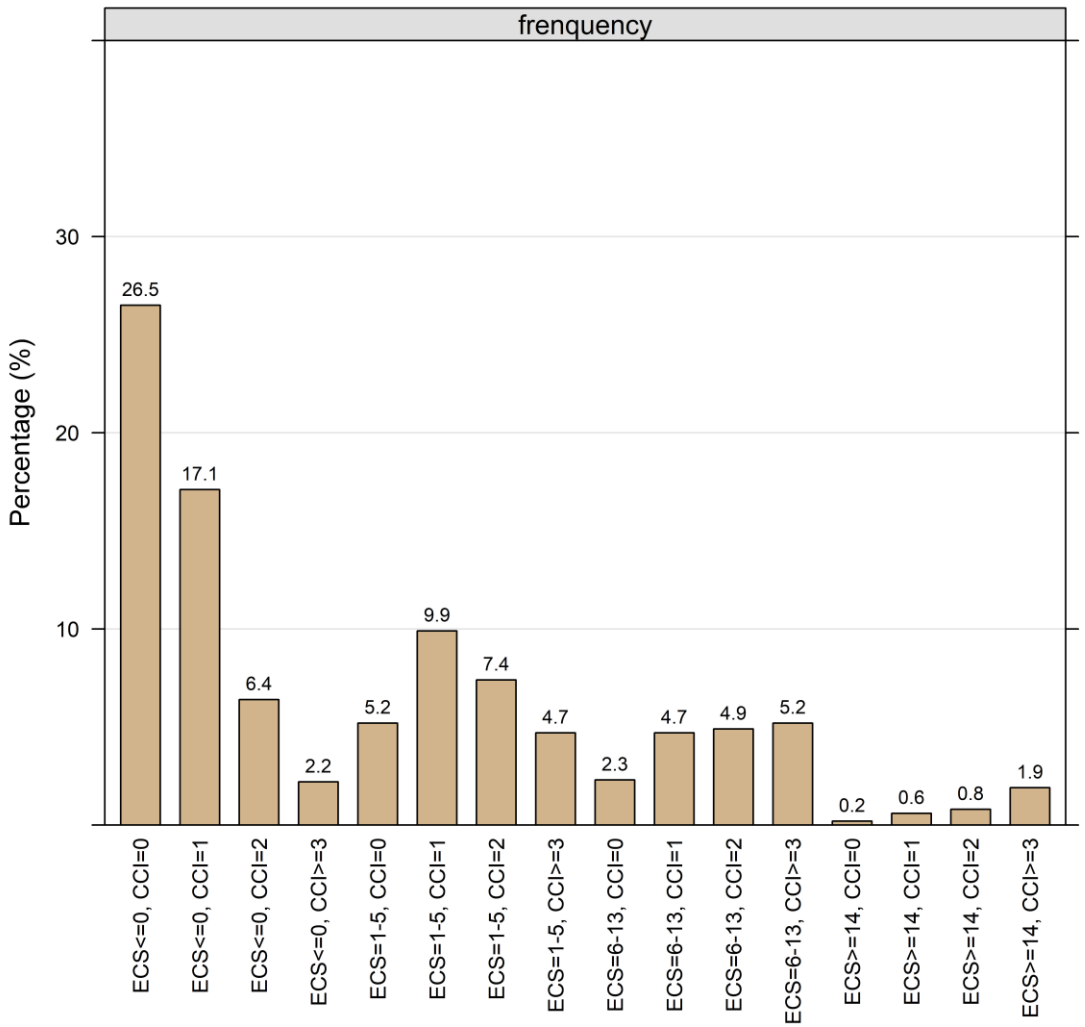


Table 8.2: Proportion of patients admitted for ACS undergoing (a) PCI and (b) CA, by two different comorbidity indices: National Inpatient Sample, USA, 2004-2014.

(a) PCI			**Charlson Comorbidity Index (CCI)**				
			0	1	2	3+	
			2,466,301	*2,328,309*	*1,406,418*	*1,000,873*	
Elixhauser Comorbidity Score (ECS)	<=0	*3,761,881*	57.43	47.15	36.33	30.39	*50.3%*
	1-5	*1,963,794*	43.46	37.94	30.95	25.82	*35.0%*
	6-13	*1,224,718*	32.61	26.09	23.22	21.73	*24.8%*
	14+	*251,506*	20.69	19.18	19.47	17.28	*18.6%*
			53.5%	*40.7%*	*30.3%*	*24.0%*	
(b) CA			**Charlson Comorbidity Index (CCI)**				
			0	1	2	3+	
			2,466,301	*2,328,309*	*1,406,418*	*1,000,873*	
Elixhauser Comorbidity Score (ECS)	<=0	*3,761,881*	75.07	68.20	61.02	56.70	*70.3%*
	1-5	*1,963,794*	65.96	61.09	55.28	50.36	*58.6%*
	6-13	*1,224,718*	52.88	47.94	46.03	43.65	*46.7%*
	14+	*251,506*	41.39	39.97	40.15	36.19	*38.2%*
			72.0%	*62.5%*	*54.2%*	*47.0%*	

Table 8.3: Proportion of patients admitted for ACS encountering (a) death, (b) major bleeding, (c) MACCE, by two different comorbidity indices: National Inpatient Sample, USA, 2004-2014.

			Charlson Comorbidity Index (CCI)				
(a) Death			0	1	2	3+	
			2,466,301	*2,328,309*	*1,406,418*	*1,000,873*	
Elixhauser Comorbidity Score (ECS)	<=0	*3,761,881*	1.88	3.23	3.88	3.63	*2.6%*
	1-5	*1,963,794*	6.67	6.34	6.08	5.76	*6.3%*
	6-13	*1,224,718*	11.46	11.88	11.10	9.51	*10.9%*
	14+	*251,506*	15.52	17.58	15.82	15.12	*15.8%*
			3.3%	*5.7%*	*7.0%*	*8.1%*	

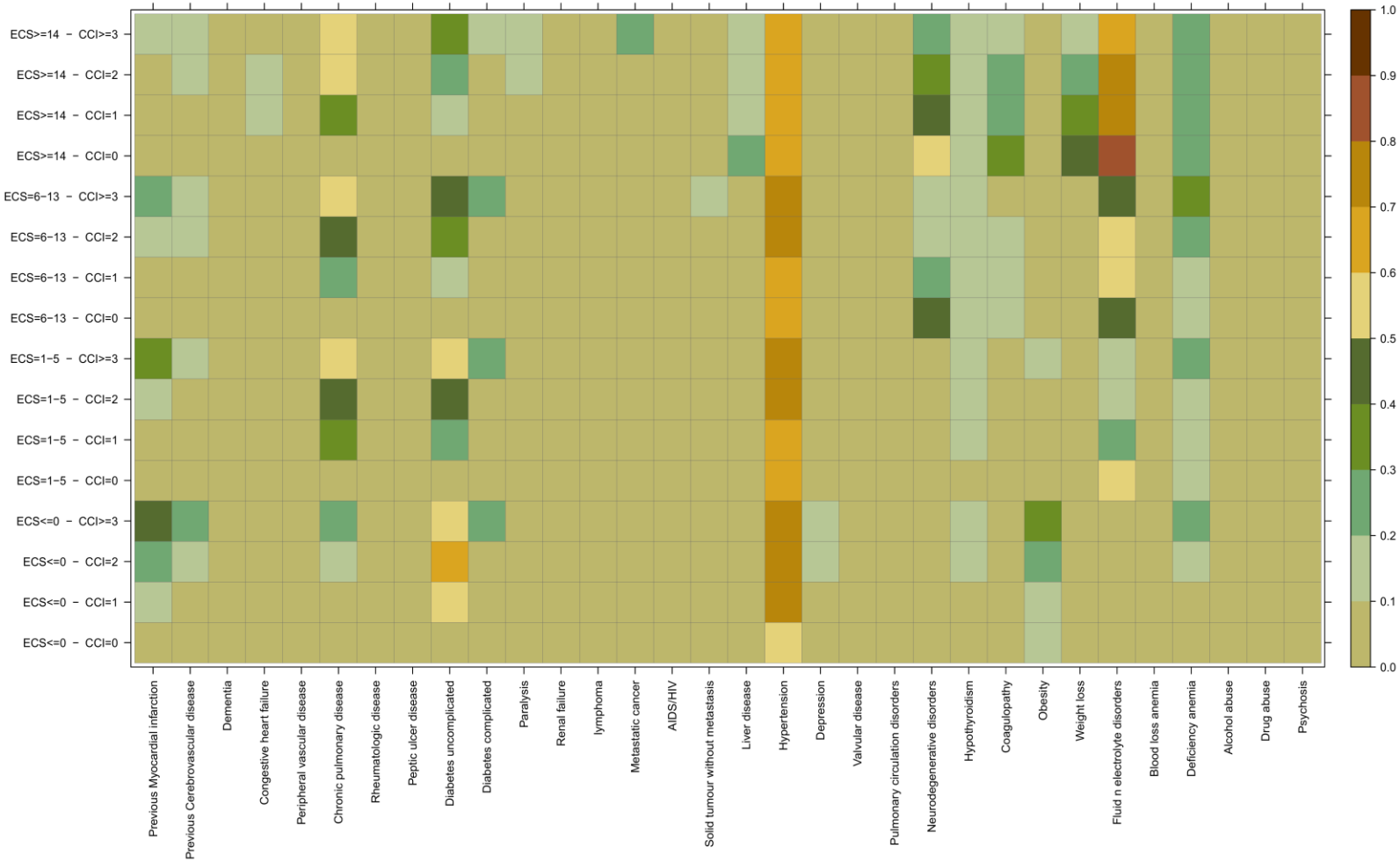
			Charlson Comorbidity Index (CCI)				
(b) Major bleeding			0	1	2	3+	
			2,466,301	*2,328,309*	*1,406,418*	*1,000,873*	
Elixhauser Comorbidity Score (ECS)	<=0	*3,761,881*	3.13	3.58	4.04	4.54	*3.5%*
	1-5	*1,963,794*	6.10	5.33	5.00	5.33	*5.4%*
	6-13	*1,224,718*	7.05	7.21	6.99	6.60	*6.9%*
	14+	*251,506*	10.35	9.59	10.95	9.18	*10.0%*
			3.9%	*4.7%*	*5.4%*	*6.1%*	

			Charlson Comorbidity Index (CCI)				
(c) MACCE			0	1	2	3+	
			2,466,301	*2,328,309*	*1,406,418*	*1,000,873*	
Elixhauser Comorbidity Score (ECS)	<=0	*3,761,881*	3.58	5.04	5.59	5.44	*4.4%*
	1-5	*1,963,794*	9.72	8.76	8.24	7.90	*8.6%*
	6-13	*1,224,718*	15.86	15.49	14.59	13.38	*14.6%*
	14+	*251,506*	20.69	22.38	20.68	22.14	*22.2%*
			5.4%	*8.0%*	*9.5%*	*11.4%*	

8.4.4 Comorbidity Distribution

The Heat map (**Figure 8.3**) illustrates the distribution of the 32 comorbidities that make up the CCI and ECS, in the different ECS/CCI combinations. Overall, most comorbidities had a relatively low prevalence (less than 0.1) across the 16 subgroups identified apart from hypertension, fluid-electrolyte disorders (LYTES), diabetes uncomplicated (DM) and CPOD. Hypertension was highly prevalent in all subgroups; LYTES had a high prevalence in four subgroups having ECS≥14; DM existed in each subgroup except those with CCI=0 and had the highest proportion in ECS≤0/CCI=2 subgroup; CPOD mainly presented in subgroups with CCI≥2. It also can be seen that two cohorts with the highest disagreement (ECS≤0/CCI≥3 and ECS≥14/CCI=0) showed greatest differences from other subgroups with respect to comorbidity prevalence: the ECS≤0/CCI≥3 combination subgroup had higher proportions than other subgroups for comorbidities such as complicated diabetes , depression and obesity. The ECS≥14/CCI=0 subgroup similarly had a different comorbidity profile than other groups, with the prevalence of liver disease, coagulopathy and weight loss relatively higher compared to other subgroups.

Figure 8.3: Distribution of the 32 comorbidities that make up the CCI and ECS.



8.4.5 Statistical Analysis

Figure 8.4 and **Table 8.4a and 8.4b** display the associations between the 16 combination categories and the receipt of invasive treatments using multivariable analysis. As comorbidity burden among the 16 subgroups increased, decreasing odds of the utilisation of PCI or CA was observed. For example, subgroup ECS=6-13/CCI=2 had 68% decrease (OR 0.32, 95%CI 0.31-0.33) in the odds of receipt of PCI, compared to the reference subgroup (ECS≤0/CCI=0), while subgroup ECS≥14/CCI≥3 had 79% decrease (OR 0.21, 95%CI 0.20-0.22). **Figure 8.5** displays the associations between the 16 combination categories and clinical outcomes. From the overall 16 subgroups, as the categories became increasingly comorbid, clinical outcomes worsened, whilst this trend was not found within every four subgroups when ECS kept the same except for the four subgroups in ECS≤0. For example, the cohort with ECS≥14/CCI≥3 had an over 5-fold increase (OR 5.82, 95%CI 5.59-6.60) in the odds of MACCE compared to subgroup ECS≤0/CCI=0. The outcomes associated with other combinations of ECS and CCI are shown in **Table 8.5a-c**.

Table 8.4: Association between Elixhauser/Charlson subgroups and recipient of treatments (a) PCI and (b) CA with ACS diagnosis (adjusted odds ratio, 95% confidence intervals †).

(a) PCI		**Charlson Comorbidity Index (CCI)**			
		0	1	2	3+
Elixhauser Comorbidity Score (ECS)	<=0	*	0.76 (0.75, 0.77)	0.53 (0.52, 0.54)	0.41 (0.39, 0.42)
	1-5	0.70 (0.68, 0.72)	0.59 (0.57, 0.60)	0.45 (0.43, 0.46)	0.35 (0.34, 0.36)
	6-13	0.49 (0.47, 0.50)	0.37 (0.36, 0.38)	0.32 (0.31, 0.33)	0.29 (0.28, 0.30)
	14+	0.30 (0.27, 0.33)	0.26 (0.24, 0.27)	0.24 (0.23, 0.26)	0.21 (0.20, 0.22)

(b) CA		**Charlson Comorbidity Index (CCI)**			
		0	1	2	3+
Elixhauser Comorbidity Score (ECS)	<=0	*	0.85 (0.84, 0.87)	0.69 (0.67, 0.71)	0.57 (0.55, 0.59)
	1-5	0.87 (0.84, 0.89)	0.74 (0.72, 0.75)	0.61 (0.59, 0.62)	0.49 (0.47, 0.51)
	6-13	0.56 (0.54, 0.58)	0.49 (0.47, 0.51)	0.45 (0.44, 0.47)	0.39 (0.37, 0.41)
	14+	0.38 (0.34, 0.41)	0.35 (0.32, 0.36)	0.34 (0.31, 0.36)	0.28 (0.27, 0.29)

*Reference is CCI=0; ACS: acute coronary syndrome; PCI: percutaneous coronary intervention; CA: coronary angiography. † Adjustment for age, gender, ethnicity.

Figure 8.4: The associations between the 16 combination categories and the receipt of invasive treatments.

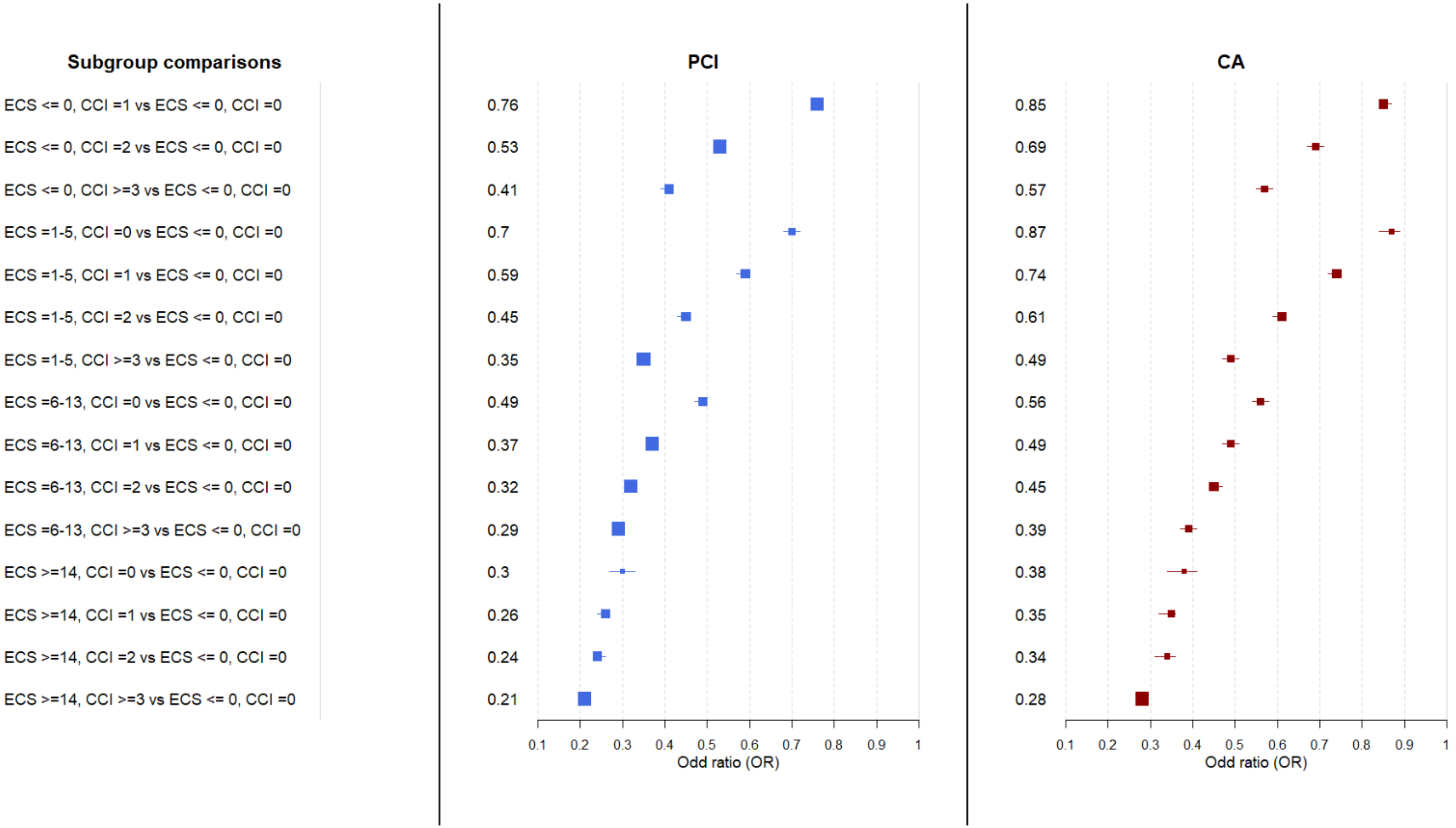
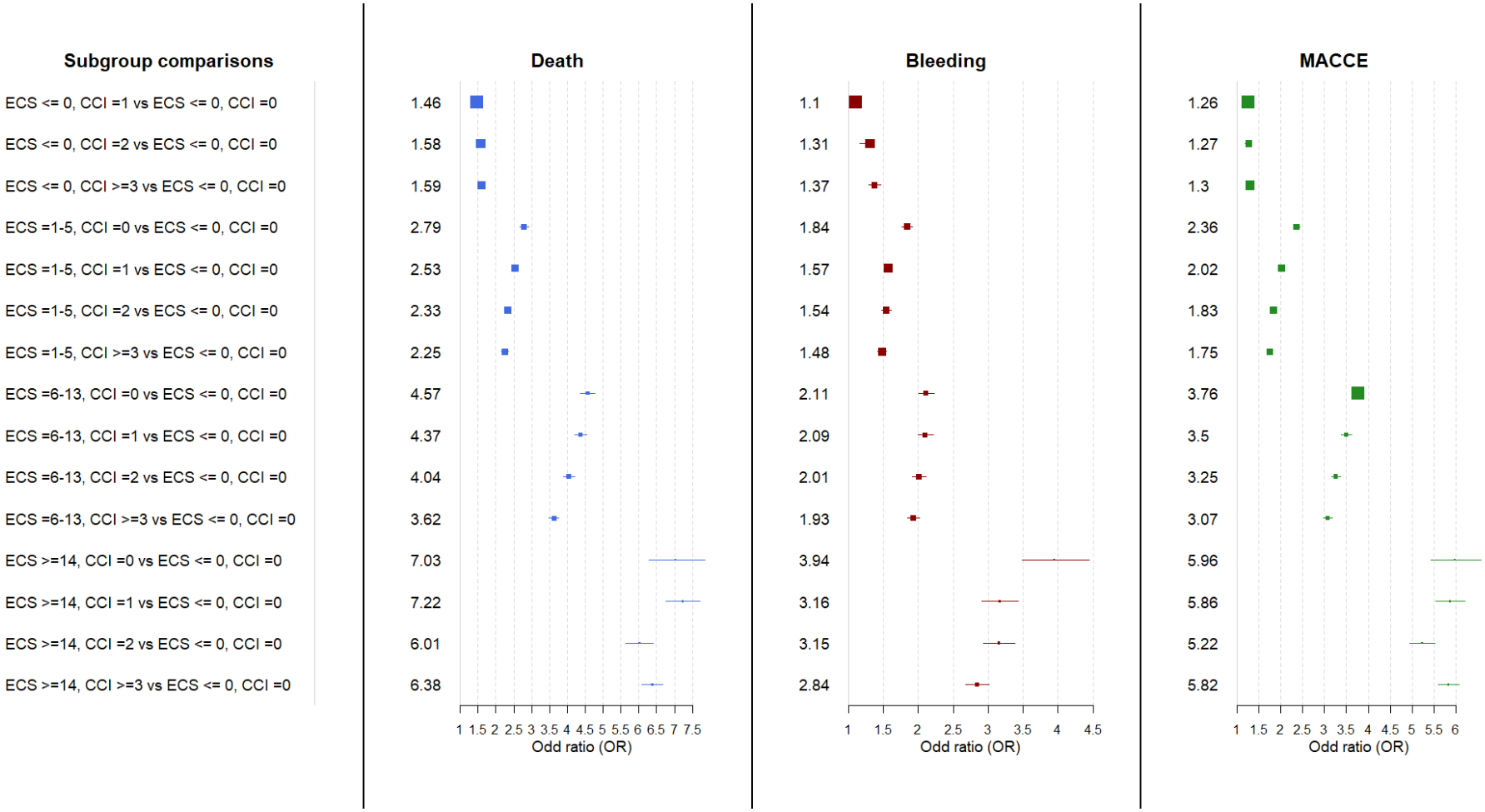


Table 8.5: Association between Elixhauser/Charlson subgroups and in-hospital clinical outcomes (a) death, (b) major bleeding and (c) MACCE with ACS diagnosis (adjusted odds ratio, 95% confidence intervals §).

(a) Death		**Charlson Comorbidity Index (CCI)**			
		0	1	2	3+
Elixhauser Comorbidity Score (ECS)	<=0	*	1.46 (1.41, 1.50)	1.58 (1.52, 1.65)	1.59 (1.53, 1.68)
	1-5	2.79 (2.67, 2.91)	2.53 (2.44, 2.62)	2.33 (2.24, 2.42)	2.25 (2.16, 2.35)
	6-13	4.57 (4.36, 4.78)	4.37 (4.20, 4.55)	4.04 (3.88, 4.20)	3.62 (3.48, 3.76)
	14+	7.03 (6.29, 7.84)	7.22 (6.77, 7.70)	6.01 (5.64, 6.40)	6.38 (6.09, 6.68)
(b) Major bleeding		0	1	2	3+
Elixhauser Comorbidity Score (ECS)	<=0	*	1.10 (1.06, 1.13)	1.21 (1.16, 1.26)	1.37 (1.29, 1.46)
	1-5	1.84 (1.76, 1.92)	1.57 (1.52, 1.63)	1.54 (1.47, 1.61)	1.48 (1.42, 1.54)
	6-13	2.11 (2.01, 2.23)	2.09 (2.00, 2.22)	2.01 (1.92, 2.11)	1.93 (1.84, 2.20)
	14+	3.94 (3.49, 4.45)	3.16 (2.91, 3.43)	3.15 (2.93, 3.38)	2.84 (2.68, 3.01)
(c) MACCE		0	1	2	3+
Elixhauser Comorbidity Score (ECS)	<=0	*	1.26 (1.23, 1.33)	1.27 (1.20, 1.33)	1.30 (1.26, 1.35)
	1-5	2.36 (2.29, 2.44)	2.02 (1.96, 2.08)	1.83 (1.77, 1.89)	1.75 (1.69, 1.82)
	6-13	3.76 (3.62, 3.91)	3.50 (3.39, 3.62)	3.26 (3.16, 3.37)	3.07 (2.97, 3.17)
	14+	5.96 (5.42, 6.57)	5.86 (5.54, 6.20)	5.22 (4.94, 5.51)	5.82 (5.59, 6.06)

Figure 8.5: The associations between the 16 combination categories and clinical outcomes.



8.5 DISCUSSION

The current analysis provides an overview of how two different measures of comorbidity burden, ECS and CCI scores overlap in a national population of over 7 million ACS patients hospitalised in the US, and whether they identify the same patient groups as being severely comorbid. It is shown that generally the agreement between the two measures of comorbidity is relatively poor, with a Cohen's kappa of 0.183. Even in the patient population that was identified as having a low burden of comorbidity by ECS (≤0), only half of these patients were defined as having low comorbidity burden by CCI (=0), with 4% of this population defined as severe comorbidity burden by CCI. Similarly, in patients defined as having the most severe comorbidity phenotype by ECS (ECS≥14), only half of patients had severe comorbidity burden as defined by CCI, with 5% being in the lowest comorbidity category of CCI. It shows that these 16 distinct combinations of ECS/CCI have very different clinical characteristics, comorbidity profiles, utilisation of treatments and clinical outcomes.

International guidelines, such as those derived from the ESC recommend that comorbidity burden is considered in the decision-making processes in guiding the treatment of ACS patients [87]. However, such guidelines fall short in defining how comorbidity burden should be defined, what measures for the overall burden of comorbidity should be used and whether they have similar results of identification. ECS and CCI are two well-established and commonly used measures to define comorbidity burden, many studies have investigated the prognostic impact of CCI or ECS in patients' outcomes with a variety of diseases [166, 178], and some authors also compared their predicted performance in different populations [82, 84]. However, there have been no prior studies to investigate whether these two scoring systems have agreed with each

other on identifying the same patients as being comorbid, and no research to explore the degree of agreement between these two measures of comorbidity. It reports that there was poor agreement (Cohen's κ =0.183) between ECS and CCI, with only half of the patients (53.0%) classified as severely comorbid by ECS (ECS≥14) were also severely comorbid in CCI (≥3). Similarly only half of the patients (50.8%) defined as having a low comorbidity burden by ECS also had a low comorbidity burden by CCI. Part of this may relate to the fact that each scoring system considers different comorbid conditions, as CCI includes 17 comorbidities and ECS contains 29 comorbidities. Nevertheless, there is significant overlap in the type of comorbid conditions captured by each scoring system. Another difference that may account for the relatively poor agreement between the two scoring systems is that comorbid conditions are weighted very differently in the two scoring systems. For example, congestive heart failure is scored as 1 in CCI whereas it is scored as 7 in ECS, whereas diabetes is scored as 0 in ECS and 1 or 2 in CCI depending on whether there is end organ damage. This data has significant implications for the consideration of comorbidity burden and how it is defined. It shows that using different measures of comorbidity burden will define different groups of patients as severely comorbid, which may impact on physician treatment choices and therefore prognosis differentially. Future guidelines may need to provide greater clarity around what is meant by significant comorbidity burden or use combinations of different measures of comorbidity burden such as ECS and CCI.

When combined, different combinations of ECS/CCI categories had different clinical phenotypes with different utilisation of invasive management and differing clinical outcomes post-ACS. Across the 16 combination cohorts, most comorbidities had a relatively low prevalence apart from hypertension, LYTES, DM and CPOD that had high prevalence across all 16 groups.

Nevertheless, the 16 groups of patients identified by different combinations of CCI and ECS had very different comorbidity profiles, for example, the ECS≥14/CCI=0 subgroup had a greater prevalence of liver disease, coagulopathy and weight loss (ECS=6) compared to other groups. Other comorbidities such as complicated diabetes, depression and obesity were more commonly seen in the subgroup ECS≤0/CCI≥3. It was found in this analysis that not only when ECS was unchanged, the odds of the utilisation of PCI or CA decreased with increases in the comorbidity burden identified by CCI within every four subgroups, but also from the overall 16 subgroups (comorbidity identified by ECS), when the comorbidity burden increased, decreasing odds of the utilisation of PCI or CA were observed. These results are consistent with previous studies [108] that indicated higher comorbid patients were less likely to receive invasive strategies than lower comorbid ones. The differences in the comorbid profiles of each different CCI/ECS category may explain the major differences in the proportion of patients receiving invasive management across each group, with the adoption of invasive management decreasing with increasing comorbidity burden. For example, the proportion of patients receiving CA in the lowest ECS/CCI combination (ECS≤0 and CCI=0) was more than twice that of the most severe comorbid phenotype (ECS≥14/CCI≥3) (75.07% vs 36.19%). Similarly, very different clinical outcomes based on different ECS/CCI category combinations were observed, with worsening clinical outcomes associated with more severe combinations of ECS/CCI from an overall view. For example, the most severe comorbidity burden subgroup (ECS≥14/CCI≥3) had around eight times greater rates of mortality than the lowest one (ECS≤0/CCI=0) (15.12% vs 1.88%). This trend has consistency with previous chapters that found patients with higher ECS comorbidity burden had a worse prognosis. However, the trend was different within subgroups identified

by CCI when ECS was unchanged except for the four subgroups in ECS≤0. Part of this may be related to the poor agreement between CCI and ECS due to the fact that two comorbidity measures include very different numbers and types of comorbidities and even the same comorbidity has different weights, which may result in the same patients with mild CCI burden being classified into the severe ECS category.

8.6 LIMITATIONS

This present study provides the first comprehensive overview of the level of the agreement between ECS and CCI measures of comorbidity burden in identifying comorbidity severity in ACS patients. The analyses results deliver reliable estimates with high accuracy in a national cohort. There are also limitations mainly from the administrative dataset [179, 180]. The database does not capture the Charlson comorbidities whilst includes Elixhauser comorbidities, the Charlson comorbidities that were not included in Elixhauser had to be extracted relying on ICD-9-codes. Additionally, the database also does not measure the severity of the individual comorbidities or how long the patients have had them, which might cause a bias in the process of merging the same comorbidities from CCI and ECS. Furthermore, the NIS only captures in-hospital outcomes and so this analysis cannot inform around post-discharge events.

8.7 CONCLUSION

This paper investigates the degree of agreement between two well-established measures of comorbidity burden, as well as treatments and outcomes in national cohort of ACS patients. It reports that the agreement between ECS and CCI categories in defining comorbidity was generally poor,

where different groups of patients will be identified as being severely comorbid depending on the classification system used. Different combinations of ECS/CCI categories have different distinct comorbidity phenotypes with differences in both their treatments and clinical outcomes. This work identifies the need for consensus to describe comorbidity, particularly when different measures identify different groups of patients as being multimorbid. Utilising both ECS and CCI measures together may facilitate making more precise medical decisions when identifying the comorbidity burden level or risk classification in ACS patients.

Chapter 9 - Discussion

General Discussion

9.1 INTRODUCTION

This PhD thesis focused on comorbidity burden and ACS prognosis. My work has identified common comorbidity measures through systematic review used in previous ACS prognostic studies; investigated the prognostic value of comorbidity measures in predicting clinical outcomes and receipt of invasive strategy; studied the performance of two commonly used comorbidity measures in predicting ACS clinical outcomes in the risk-adjustment models; explored their degree of agreement with each other and the difference in clinical characteristics, comorbidity profiles, treatments and ACS outcomes in their combination groups. As all the results have been discussed in detail in the respective chapters of this thesis, the focus of this chapter is to provide an overview of the important findings synthesized from previous chapters and to discuss implications for future research.

9.2 SUMMARY OF MAIN FINDINGS

There were currently five comorbidity measures developed and used to predict the prognosis of ACS patients. In a series of parallel analyses of ACS patients in the NIS dataset, It was found that higher comorbidity scores on both the CCI and ECS/NEC measures were each associated with worse clinical outcomes and lower likelihood of receiving invasive treatment. The ECS appeared to be marginally better at predicting ACS outcomes and use of treatments. However, the ECS and CCI did not necessarily classify the same patients as having high levels of comorbidity: a finding that implies that the choice of comorbidity measure could be important when used as part of individual clinical decision-making.

9.2.1 Approaches to Measuring Comorbidity and Their Association with ACS outcomes

Chapter 3 was focused to identify existing measures used to define comorbidity burden in ACS patients and report the association between comorbidity burden and ACS outcomes. The main findings of the study showed that eight studies were identified with a total of five different types of comorbidity measures used and CCI is the most widely used measure to investigate the prognostic impact of comorbidity burden on ACS outcomes, four studies applied different versions of the CCI method while ECS was not found in previous ACS prognosis studies. These previous studies reported that increasing comorbidity burden regardless of how it was defined had an association with an increased risk of a variety of ACS outcomes in the short-term (in-hospital or 6-month readmission ACS) or long-term (one-year or 24-month mortality). The review also observed some model comparisons studies that indicated ECS might perform better than CCI in prediction models for ACS outcomes.

9.2.2 Prognostic Impacts of CCI and ECS on ACS outcomes

Chapters 5 & 6 examined the impact of comorbidity burden defined by the two most commonly used comorbidity measures on the prognosis of treatment and clinical outcomes in ACS patients from a national perspective. Comorbid burden had increased amongst ACS patients over 11 years, with the percentage of patients with higher comorbid burden increasing. For example, the proportion of patients with severe CCI comorbidity burden almost doubled from 10.8% in 2003 to 18.1% in 2014, meanwhile, almost one in five patients with ACS had 5 or more Elixhauser comorbidities in 2014 which was four times than it was in 2004. Patients with heavier comorbid burden were more likely to have a worse prognosis for the outcomes of MACCE, mortality, acute ischemic

stroke and major bleeding regardless of whether the burden was defined by the severity of comorbidity (CCI and ECS) or the number of comorbidities (ECS). This association still existed even after adjustment for differences in baseline variables and receipt of treatments. For example, the risk of mortality increased 80% in patients with CCI≥3 compared to patients with no comorbidities (CCI=0), the risk of MACCE in ECS≥14 was 4.65 times than that in ECS<0 while the risk of major bleeding in NEC≥5 was almost 3-fold compared to the group with no ECS comorbidity burden. However, this association was inverse in terms of the utilisation of invasive therapies, ACS patients with severe CCI comorbidity burden (CCI≥3) were least likely to receive invasive strategies, and the larger number and higher severity of ECS comorbid burden were also related to the lower rate of use of PCI or CA. Finally, these two chapters also touched on the potential economic impact of comorbid burden: longer length of stays and higher hospital healthcare cost were seen in patients with greater comorbidity.

9.2.3 Comparative Predictive Performance of CCI and ECS

Chapter 7 of this thesis was focused to compare the performance of ECS and CCI methods in predicting ACS outcomes by applying their scoring systems to a national database of ACS patients. This study used two forms of ECS and CCI scores (continuous and categorical), expanded the clinical outcomes from mortality to other clinical outcomes including MACCE and major bleeding. The results showed that ECS was superior to the CCI method in predicting all in-hospital adverse outcomes examined in this thesis in the terms of discrimination and model goodness of fit, regardless of whether it was in continuous or categorical form. However, differences in model performance were often fairly modest. For instance, models using ECS for predicting MACCE had a higher degree of discrimination (C-statistics 0.776) than models that used CCI

(0.757). Meanwhile, in the ECS models, except for predicting major bleeding, models with the highest C-statistics and lowest AIC-BIC were those treating the ECS scores as a continuous variable rather than as a categorical score. Differences in C-statistics were slight.

9.2.4 Agreement Between CCI and ECS in Classifying Patients

Analysis in Chapter 8 is the first study to date to provide an overview of how two different measures of comorbidity burden overlapped in identifying the same patient groups as being comorbid using a national population of over 7 million ACS patients. It showed that, overall, the agreement between two comorbidity measures was low, with a Cohen's kappa of 0.183. Even in the groups that were identified as having the most severe comorbid burden by ECS (ECS≥14), only half of the patients were determined by CCI into the most severe comorbidity group while the other half were not in the most severe CCI groups, and 5% of them were confirmed by CCI as having no comorbidities. Results in this analysis also showed that the 16 combination subgroups of ECS/CCI were very different in clinical characteristics, comorbidity profiles, utilisation of treatments and clinical outcomes. For example, compared to the other 15 combination subgroups, the ECS≥14/CCI=0 subgroup had a greater prevalence of liver disease, coagulopathy, and weight loss. Another example, the odds of the utilisation of PCI or CA decreased with increasing comorbidity burden identified by 16 combination subgroups.

9.3 INTERPRETATION OF MAIN FINDINGS

Although five comorbidity measures were found in the systematic review, four of them were developed early using old datasets with a small sample size while the magnitude of association of comorbidity and ACS outcomes may

change due to advances in medical diagnosis and treatments [105]. Meanwhile, all measures apart from CCI were only validated in their specific populations and may not fit widely for prognosis research in other groups of patients. Even so, most identified studies that used CCI were also limited to either smaller in sample size [59] and old data [60] or community-based studies restricted to a particular geographic area [132], and clinical outcomes in those studies were limited to just mortality. Furthermore, at the time of conducting my systematic review, there was no published literature around applying ECS to investigate ACS prognosis although ECS has been accepted as an effective comorbidity measure and might be better than CCI in predicting ACS outcomes. Although two new studies [181, 182] have been published since the systematic review was concluded, neither used the ECS. One study [182] was published by Pastor in 2019 and included 520 elderly patients (>80 years) with ACS, the other [181] by Hautamäki was published in 2020 and studied 1576 ACS patients from 2015 to 2016, both of them applied the CCI to define the patients' comorbid burden. Two new studies also showed that increasing comorbidity burden irrespective of how it was measured was associated with worse ACS outcomes, which is consistent with the findings in eight identified studies. However, Pastor's study [182] categorised CCI scores into quartiles. These, cut-off values are specific to their study population limiting their value in other samples and the ability to directly compare findings across studies. These above findings from my systematic review laid the foundation for the CCI and ECS analyses. The studies around these two comorbidity measures filled this evidence gap and expanded on existing knowledge with some important results.

The CCI and ECS analyses used more than 7 million ACS hospitalisations to explore the association between the comorbidity burden and the prognosis of ACS. The results showed that the comorbidity burden of ACS patients defined

by CCI or ECS increased over years from 2004 to 2014, which extended the results from a previous study that showed the prevalence of CV risk factors in AMI patients (such as diabetes, hypertension and heart failure) increased between 1990 and 2007. These findings updated the epidemiological data in population demographics and risk factors of ACS patients.

CCI and ECS analyses reported whether it was classified by severity (CCI or ECS) or the number of comorbidities (NEC), the increasing comorbidity burden was related to the increased risk of all ACS-related outcomes in this thesis. The risk of mortality in patients with the most CCI severe comorbidities (CCI≥3) was 74% higher than that in patients without comorbidities, the risk of MACCE increased by 1.13 times with per one unit increase in CCI scores. There were previous studies that reported the higher CCI comorbid burden on ACS patients was associated with worse outcomes [54, 60, 83, 96, 124], and a new study published in 2020 [181] demonstrated that for per unit increase in CCI score, the hazard ratio of 30-day mortality for ACS patients increased by 14%, however, these studies lack generalizability compared to my study due to their smaller sample size and other limitations as previously mentioned. Most clinical outcomes in these studies were limited to mortality while my analyses contained more clinical outcomes. For example, CCI analysis showed the risk of acute ischemic stroke in CCI≥3 was 2.49 times and the risk of bleeding was 1.64 times that in CCI=0. Although my results were limited to in-hospital outcomes, the association between the CCI burden and long-term mortality (e.g. 24-months) among ACS patients has been reported by multiple studies [54, 59, 96]. Sensitivity analysis found that non-CV comorbidities in the CCI that are not routinely included in ACS prognosis scores such as cancer or moderate to severe liver disease had a greater impact on ACS outcomes compared to other comorbidities. This finding is consistent with the results of a previous study

[103], that incorporated CCI into the GRACE score to improve the prediction of mortality or future heart-related events. Meanwhile, compared with the lowest ECS comorbid burden group (ECS<0), the odds of MACCE in the highest ECS group (ECS≥14) increased by more than 4 times whilst the group with the largest number of ECS comorbidities (NEC≥5) had 2-3-fold increase in the odds of major bleeding compared to NEC=0. Previous studies have examined the association between comorbid burden and clinical outcomes of ACS. However, as mentioned earlier, most of them used CCI instead of ECS which was not applied to study the prognosis of ACS before this thesis. Although there have been several studies [82, 83, 97] that included ECS in their analysis, they lack information about prognostic impact as their research focuses were comparing the predictive performance of different comorbidities rather than the impact of comorbidity burden on ACS. One exception [101] was a two-centre study of 5275 AMI patients hospitalized in Spain, it reported that the risk of in-hospital mortality during the study period from 2003 to 2009 increased by 14% with per unit increase in the number of Elixhauser comorbidities, however, the study did not use the ECS scoring system.

Treatment is often a missing factor in prognostic studies, despite that fact that it clearly has the intention of being prognosis-altering. In the analyses of NIS data from 2004-2014, ACS patients with severe comorbidity burden (CCI≥3 and ECS≥14) were the least likely to receive invasive treatment (CA or PCI) compared with patients with fewer or no comorbidities. However, the current guidelines recommend early routine invasive treatment, especially for STEMI (in the form of PCI) and high-risk NSTEMI [24, 88, 111], and there is some evidence that the benefits from PCI in NSTEMI patients, in terms of long-term survival, were larger in those with higher comorbidity scores [110]. In a separate study [95] that developed a comorbidity measure (SCM) reported that

in-hospital revascularization was associated with reduced mortality of ACS patients with more than 2 comorbidities (SCM≥2). The evidence from the above studies showed that the actual situation of ACS patients with comorbidity burden was different from the guidelines in terms of treatment options, and the compliance with the adoption of guidelines was relatively lower, especially in patients with a high comorbid burden. It may be attributed to the belief that patients with a higher comorbidity burden are not suitable for revascularization or the risk-benefit balance in these patients is less favourable than for patients with few or no comorbidities. For example, a study showed that patients with severe comorbidity burden undergoing coronary revascularization with PCI were at greater risk of severe bleeding complications and adverse outcomes [78]. In addition, there are several reasons why ACS patients with a higher comorbidity burden have poorer outcomes, as described above, patients with more severe comorbidities are less likely to receive coronary reperfusion therapy could be one reason. Nevertheless, the CCI and ECS analyses indicated that the increased risk of adverse outcomes related to increased comorbidity burden persisted despite adjustment to treatment. As was mentioned in chapter 3, it might have other reasons such as patients with a higher comorbid burden having a longer delay in the symptom onset and admission, more complications, poorer functional recovery [49, 53, 96].

Comparison studies in the systematic review reported that ECS might outperform CCI, which was more widely used, in the prognostic impact of comorbidity burden in ACS patients. However, as mentioned earlier, these studies had their own limitations. Except for the study published in 2020, the CCI and ECS scoring systems were not used in the remaining comparison studies, although the CCI scoring system was widely used in clinical practice when these articles were produced. These studies placed the comorbidities

contained in the ECS and CCI as binary predictors (presence and absence of the comorbidity) in the models. Such an approach may favour the ECS since it includes a greater number of comorbidities than the CCI. It also results in greater over-fitting of an ECS model. In each instance, the ECS would be expected to outperform CCI. This possibility was raised in a previous study [83]. This finding promoted the comparative analysis undertaken in this thesis. My analysis summed ECS and CCI scores into a total score based on their scoring systems and applied them into the models as a predictor after adjustment to avoid this kind of bias.

The results showed that ECS remained superior to the CCI in terms of discriminative ability and model goodness of fit, regardless of whether their scores were categorised or continuous. This finding was applicable to all ACS clinical outcomes included. The results improved the limitations in previous studies and expanded their results. In addition, most previous studies focused on mortality while my research extended to other clinical outcomes (such as MACCE and major bleeding), which may contribute to a greater general understanding of the performance of comorbidity measures.

In direct head-to-head comparisons, my analyses found that the continuous ECS may outperform the categorical ECS in predicting in-hospital mortality and MACCE, which was not explored in previous studies. It was hypothesized that the possible reasons included: 1)when ECS scores are grouped into a categorical variable, information loss occurs and the statistical power of detecting the association between ECS and patient outcomes might be reduced [183], 2) the extent of variation in outcome between groups was underestimated, when choosing the cut-off values, it was assumed that individuals close to but on the opposite sides of the cut-off values were very different while they may be very similar [162]. However, the cut-points method

was validated and widely used in Elixhauser, Charlson papers and other studies. Meanwhile, my sensitivity analysis also considered the nonlinearity between comorbidity scores and outcome by adding non-linear terms (score squared and cubed) into the continuous ECS/CCI models. The effect sizes (ORs) of these non-linear terms were very close to 1 with their 95%CIs crossing 1, which indicated no strong evidence to prove the existence of a non-linear relationship between the continuous form of ECS/CCI and ACS outcomes [156].

Agreement analysis results showed that the agreement between CCI and ECS was generally low. Only half of the patients classified as severe comorbid burden by one of the comorbidity measures (ECS≥14) were also stratified as severe comorbidity by another comorbidity measure (CCI≥3), and even respectively 4.2% and 5.5% of the patients within the most severe comorbid burden were classified into the lowest comorbid burden group by another measure. Some of the potential reasons for this result may be that the comorbidities contained in ECS and CCI are quite different as CCI includes 17 conditions and ECS covers 29 comorbidities. Even so, there are still at least 12 comorbidities shared between CCI and ECS, which is a significant overlap. Furthermore, the same comorbidities were weighted very differently in the two scoring systems, for example, AIDS has a score of 0 in the ECS score which is not a high weight while it has the highest score (=6) in CCI although the prognosis of AIDS patients has been improved with the advancement of medical technology [105]. Agreement analysis yielded 16 subgroups, on the whole, the risk of clinical outcomes of ACS increased with increasing comorbidity burden in the subgroups and the more comorbid burden was related to the lower rate of utilisation of invasive treatment, this result was consistent with the previous chapters. However, It was also noticed that when the ECS remained unchanged, the relationship between the comorbidity burden and the ACS outcomes within

the subgroups identified by CCI was not as the above. Instead, patients with lower CCI comorbid burden was associated with a worse ACS prognosis. It is believed that the possible reasons might be related to the poor agreement between ECS and CCI, and also due to different combinations of ECS/CCI having very different comorbidity phenotypes. For instance, compared with other subgroups, the subgroup with ECS≥14/CCI=0 had a higher prevalence of liver disease and weight loss. Liver disease has a high score of 11 in ECS, weight loss has an ECS score of 6 while these two high-scoring comorbidities are not covered in CCI. Patients classified into this subgroup had no CCI comorbidity burden but a high score of ECS, therefore, these patients were still at a high risk of adverse outcomes compared to subgroups such as ECS≥14/CCI>0.

9.4 LIMITATIONS

The work presented in this paper provides a comprehensive overview of the relationship between the comorbidity burden in ACS patients and their prognosis. Systematic review in the thesis is the first to summarize existing evidence on the prognostic impact of comorbidity in ACS patients. Moreover, my search process was strictly carried out in accordance with updated guidelines [90] for the systematic reviews for prognostic factors studies. However, the limitations were also acknowledged in the review. In addition to the shortcomings mentioned earlier, one drawback was that the review only included eight studies which might be due to overly restrictive inclusion criteria: only studies that used the comorbidity measure and also reported the estimates of the impact of comorbidity measures on ACS prognosis were included in the review. There are many more studies that have included a measure of comorbidity (often the CCI) as a covariate or confounder in predictive models focussed on another prognostic factors such as warfarin use.

The CCI and ECS analyses illustrated the value of using the large national database to examine the temporal trends in baseline characteristics, the comorbidity burden, and to investigate the differences in clinical characteristics in different comorbidity burden subgroups, and the relationships between the comorbid burden and ACS prognosis. However, they also have some limitations. Firstly, as mentioned before, the NIS database is an administrative dataset. Coding errors (such as data that was improperly entered at the agency), underreporting of secondary diagnoses (such as incomplete data items, particularly those items not required by the agency for management), and missing data are potential sources of bias. Secondly, although the NIS database contains many information about baseline characteristics, comorbidity, procedure and in-hospital clinical outcome, some detailed data on pharmacological treatment and procedural details such as blood test, antiplatelet regime type and duration, and left ventricular is not collected. However, these data may provide additional information to help us better risk stratification of ACS patients with comorbidity burden, such as adding comorbidity measures to ACS clinical prognosis scores. Furthermore, due to the lack of long-term outcomes data in the NIS database, this limited the research methods to models for in-hospital outcomes and it was unable to conduct other models like survival analysis. Finally, the NIS data does not capture the exact cause of death, nor lacks formal adjudication of outcomes, this may cause unmeasured or unidentified confounders, the possibility of adverse effects of these confounders on the results cannot be ruled out. However, the NIS has captured a wide range of ECS comorbidities and CCI comorbidities also have ICD-9-CM code guides, which may help alleviate this bias.

Comparison analysis provides convincing and important information for defining what comorbidity index should be preferred to be used to measure the

comorbidity burden of ACS patients, compared to previous comparison studies. However, in addition to the aforementioned limitations, the results found that the continuous ECS model was better than its categorical model in terms of in-hospital mortality and MACCE. This conclusion was based on the assumption that the continuous form of the ECS scores had a linear relationship with outcomes. In view of the complexity of the dataset, thus limiting the ability to explore nonlinearity. Agreement analysis is the first study to examine the agreement between ECS and CCI in the classification of comorbidity burden in ACS patients. In addition to the limitations mentioned before, the agreement analysis also has its limitations accordingly. This analysis needed to merge the comorbidities that overlap in the two comorbidity measures. Although the NIS has already included ECS comorbidities, it was still needed to use ICD-9-CM codes to extract those CCI comorbidities that are not shared with the ECS, this may lead to bias in the results due to codes. In addition, the database does not measure the severity of individual comorbidities or the specific information about suffering from these diseases, which may lead to bias when combining the same comorbidities from the two comorbidity measures.

9.5 IMPLICATIONS

The results from the studies conducted in this thesis present novel information on various aspects of the impact of comorbidity burden on the prognosis of ACS patients, which may have important implications.

The proportion of ACS patients presenting with multiple comorbidities clearly increased between 2004 and 2014 and there is good reason to suspect that this trend has continued to the present [184, 185]. For example, a study from China reported that the proportion of first stroke patients with severe and very severe comorbidity increased 12.9% from 2010 to 2020 [184]. In this

context, research on the impact of comorbidities on ACS prognosis and how best to capture it becomes important. The CCI and ECS are the most widely used comorbidity scores to measure the comorbid burden. However, apart from the ECS study in this thesis, studies investigating the application of ECS in the prognosis of ACS remain uncommon: none were found in the updated systematic review, however comparison studies in the review and my comparison analysis both reported that the performance of the ECS models in predicting ACS outcomes may be better than CCI models. Therefore, for the purpose of quantifying potential risks of adverse outcomes, it is suggested that the ECS be considered by clinicians and services.

Next, CCI and ECS have a relatively low agreement in stratifying the comorbid burden of ACS patients, and the possible reasons have been discussed above. Different comorbidity measures could classify the same patients into different groups of comorbid burden, which may influence doctors' decisions on treatments and thus affect their prognoses. This finding has significant implications for defining the comorbidity burden of ACS patients and warrants replication in more recent large-scale, representative data and fuller exploration of the implications for individual clinical-decision-making. Given that the choice of comorbidity measure could affect individual patient outcomes, there may be a need for a consensus among relevant international professional organisations and societies. Future guidelines may need to explain the meaning of severe comorbidity burden more clearly. Clinicians may need to consider the use of a combination of different comorbidity measures (such as ECS and CCI) when stratifying patients' risk to guide the decision-making of treatments.

Furthermore, as mentioned early, the current guidelines [24, 88, 111] recommend using early routine invasive treatment, especially for STEMI and high-risk NSTEMI patients, and there were also studies [110] that reported that

the use of PCI was associated with a better prognosis compared to conservative treatment, this advantage increased with increase the comorbid burden. However, CCI and ECS analyses found invasive treatments in the forms of CA and PCI were underutilised, especially in patients with a higher comorbid burden, which implied compliance with the adoption of guidelines is relatively low. This finding suggests that clinicians perhaps should consider conducting invasive management for such patients instead of unwillingness to provide diagnostic angiography and revascularization. One recommendation is to establish more detailed guidelines in the future for the management of invasive treatment for patients with a high comorbid burden, such as considering addressing comorbidities in parallel rather than in isolation, performing a comprehensive assessment by a multidisciplinary team and targeting to tailor pharmacotherapy or revascularization for these high-risk patients.

Meanwhile, it was hypothesized that the lack of aggressive treatment (PCI or CA) might have an impact to some extent on the increased risk of adverse outcomes in ACS patients with a higher comorbid burden. However, CCI and ECS analyses showed that measure of comorbidities, even after adjustment for treatments, were still highly predictive of worse outcomes, indicating that comorbidity measure can identify patients with high risk, thus allowing better estimation of individual prognosis. This finding provided useful information regarding the impact of the comorbidity measure on ACS prognosis. It suggests CCI or ECS should be considered by clinicians in the prognostic prediction of ACS patients to guide the decision making, ensuring the benefit derived from each treatment in each patient, optimising the resources and avoiding futility.

9.6 FUTURE RESEARCH

As increased risk of adverse events in ACS patients with high levels of

comorbidity persisted after adjustment for treatment. This suggests that current patterns of access to, and effectiveness of, treatment in this subpopulation are insufficient to entirely offset the increased risk of in-hospital adverse event. Research to understand the effects of improving access to the most effective invasive techniques, as well as additional innovations tailored to those with high levels of comorbidity may be useful.

Apart from the reasons mentioned early, co-existent frailty of patients might be one relevant factor. According to current medicine, frailty can be defined as a state of impairment in multiple organ systems causing decreased physiologic reserve and increased vulnerability to stressors [186]. Frailty is distinct from comorbidity, although they are inter-related and often overlap in the elderly and lead to impairment in functional status as well as worse prognosis [187]. It is an obvious confounder for comorbidity study. There is substantial evidence supported the value of frailty as a prognostic factor in patients with CV diseases [188, 189]. Hence, future research can fall in the area that investigating intersection of comorbidity and frailty in the risk prediction of ACS patients which might provide valuable prognostic information and improve decision-making.

As above, clinicians were advised to adopt the invasive strategies on ACS patients with comorbid burden. However, invasive treatment decision in patients with a high comorbid burden is not straightforward with a great challenge, mainly because of increased operative risk. While there were studies that showed such patients at higher comorbid burden were likely to benefit from an early invasive approach, there were also evidence which demonstrated they were at an increased risk of operative complications such as major bleeding [78]. Therefore, it suggests clinicians need to balance between “increased risk of complications after invasive treatment” and “benefit of treatments in comorbid

patients" when formulating treatment strategies, which also inspired the interest in exploring the critical level between benefits of treatments and risk in comorbid patients. Future research may require the development of more targeted models to define whether there is a level of comorbidity whose benefit of invasive strategies outweighs the risk in comorbid patients, and identify where this level of comorbidity is.

In addition, although my CCI study proved that CCI was one strong predictor in the prognosis of ACS patients, a study [103] identified in my review demonstrated that adding CCI score to the commonly used ACS prognosis scores (such as GRACE) could improve the prediction of cardiac-related events and mortality. However, since the NIS database does not capture clinical data (such as heart rate/pulse and Killip class) that is contained in GRACE scoring, it limited us to conduct in-depth exploration. Therefore, consideration regarding comorbidity measures with prognostic impact and often not included in commonly used risk scores is important, if the data allows, future research can incorporate CCI or ECS methods into prognosis scores of ACS patients (such as GRACE score or thrombolysis in myocardial infarction (TIMI) risk score) to see if the performance of the risk stratification model is improved, thereby helping to guide the management of ACS patients in clinical practice.

CCI and ECS analyses used comorbidity scores as the continuous and categorical variables in the logistic regression models, respectively. In the models with the continuous form of comorbidity scores, although the assumption of linearity to logit was checked by adding simple non-linear terms into models and found that there was no strong evidence for the existence of nonlinearity, more complex models were limited for further exploration due to the complexity of the dataset. Future research could consider more complex functional models in simple databases, such as fractional polynomials or

splines, to explore the potential possibility of a nonlinear relationship between comorbidity scores and ACS prognosis. Comparative analysis showed the ECS has a better performance than CCI in predicting in-hospital outcomes. A previous study [97] reported a similar result in predicting long-term (one-year) mortality, however, this study still had the limitations mentioned earlier. Therefore, those findings promote further research on the performance comparison of CCI and ECS in predicting post-discharge or long-term outcomes.

9.7 CONCLUSION

ACS patients admitted to hospital are increasingly likely to have multiple comorbidities. Comorbidity burden is of major importance for the care and outcomes of patients with ACS. Patients with higher levels of comorbidity have a higher risk of a range of poor outcomes, including in-hospital mortality, MACCE and major bleeding. Part, but not all, of this may be explained by the lower likelihood of receiving invasive intervention although the utilisation has been increasing over recent years. Clinicians and services are encouraged to incorporate comorbidity measures in individual risk prediction and to balance carefully the potential for invasive strategies to be safely and effectively applied to patients with comorbidities, against the increased risk of complications. Of the two most commonly used and validated measures, the ECS method has not been as widely used as the CCI in studies of ACS prognosis. However, work in this thesis suggests that the ECS may outperform the CCI in predicting future outcomes in ACS and should therefore be considered for adoption in practice. At the level of the individual patient, this thesis draws attention to the fact that the ECS and CCI differ in their contents and, importantly, appear to classify a different set of patients as having the "high" levels of comorbidity burden. The extent of such disagreement in the classification of individual patients should

ideally be replicated in independent studies, and the potential consequences of misclassification fully explored. Consensus on the operational definition of "high" comorbidity may be needed. Future research may focus on developing models to define a level of comorbidity where the benefit of treatments outweighs its operative risk; investigating the intersection of comorbidity and frailty in ACS prognosis; identifying whether incorporating the CCI or ECS into ACS risk scores can improve the performance of risk predictive models; exploring the possibility of a nonlinear relationship of comorbid burden with ACS outcomes; comparing the performance of the CCI and ECS in predicting long-term ACS outcomes.

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Appendix

A set of appendices

APPENDIX I: SUPPLEMENTARY TABLES

Appendix Table 3.1: Searching strategies.

Searching strategy for Medline (From inception to 2021).	
#	**Searches**
1	Acute Coronary Syndrome/
2	(coronary adj3 syndrome*).ti,ab,kf.
3	acute coronary.ti,ab,kf.
4	exp Myocardial Infarction/
5	heart attack.ti,ab,kf.
6	((cardiac or heart) adj3 infarct*).ti,ab,kf.
7	(myocard* adj3 infarct*).ti,ab,kf.
8	Coronary Thrombosis/
9	(coronary adj3 thromb*).ti,ab,kf.
10	(ami or acs or mi).ti,ab,kf.
11	exp Angina, Unstable/
12	unstable angina.ti,ab,kf.
13	unstable coronary.ti,ab,kf.
14	non st segment.ti,ab,kf.
15	without st segment.ti,ab,kf.
16	non-Q-wave.ti,ab,kf.
17	NSTEMI.ti,ab,kf.
18	(ST adj2 elevat* adj4 (myocardial infarction* or MI)).ti,ab,kf.
19	stemi.ti,ab,kf.
20	((comorbid* or co-morbid*) adj3 (predict* or risk* or score* or index* or rule* or algorithm* or model* or measure*)).mp.
21	((multimorbid* or multi morbid*) adj3 (predict* or risk* or score* or index* or rule* or algorithm* or model* or measure*)).mp.
22	((multiple or concurrent*) adj2 (disease* or condition* or illness* or diagnos* or morbid*) adj3 (predict* or risk* or score* or index* or rule* or algorithm* or model* or measure*)).mp.
23	((multipatholog* or multi patholog*) adj3 (predict* or risk* or score* or index* or rule* or algorithm* or model* or measure*)).mp.
24	Elixhauser.mp.
25	Charlson.mp.

Searching strategy for Embase (From inception to 2021).	
#	**Searches**
1	acute coronary syndrome/
2	(coronary adj3 syndrome*).ti,ab,kw.
3	acute coronary.ti,ab,kw.

4	exp Heart Infarction/
5	heart attack.ti,ab,kw.
6	((cardiac or heart) adj3 infarct*).ti,ab,kw.
7	(myocard* adj3 infarct*).ti,ab,kw.
8	Coronary Artery Thrombosis/
9	(coronary adj3 thromb*).ti,ab,kw.
10	(ami or acs or mi).ti,ab,kw.
11	Unstable Angina Pectoris/
12	unstable angina.ti,ab,kw.
13	unstable coronary.ti,ab,kw.
14	non st segment.ti,ab,kw.
15	without st segment.ti,ab,kw.
16	non-Q-wave.ti,ab,kw.
17	NSTEMI.ti,ab,kw.
18	(ST adj2 elevat* adj4 (myocardial infarction* or MI)).ti,ab,kw.
19	stemi.ti,ab,kw.
20	exp comorbidity assessment/
21	((comorbid* or co-morbid*) adj3 (predict* or risk* or score* or index* or rule* or algorithm* or model* or measure* or assessment*)).mp.
22	((multimorbid* or multi morbid*) adj3 (predict* or risk* or score* or index* or rule* or algorithm* or model* or measure* or assessment*)).mp.
23	((multiple or concurrent*) adj2 (disease* or condition* or illness* or diagnos* or morbid*) adj3 (predict* or risk* or score* or index* or rule* or algorithm* or model* or measure* or assessment*)).mp.
24	((multipatholog* or multi patholog*) adj3 (predict* or risk* or score* or index* or rule* or algorithm* or model* or measure* or assessment*)).mp.

Searching strategy for Web of Science (From 2017 to 2021).

#	Searches
1	TS=(coronary near/2 syndrome*)
2	TS=(acute near/2 coronary syndrome*)
3	TS=heart attack*
4	TS=((cardiac OR heart) near/2 infarct*)
5	TS=(myocard* near/2 infarct*)
6	TS=(coronary near/2 thromb*)
7	TS=(ami OR acs OR mi)
8	TS=unstable angina
9	TS=unstable coronary
10	TS=non st segment

11	TS=without st segment
12	TS=NSTEMI
13	TS= (ST near/1 elevat* near/3 (myocardial infarction*))
14	TS= (ST near/1 elevat* near/3 MI)
15	TS=stemi
17	TS=((comorbid* OR co-morbid*) near/2 (predict* OR risk* OR score* OR index* OR rule* OR algorithm* OR model* OR measure*))
18	TS= ((multimorbid* OR multi near/0 morbid*) near/2 (predict* OR risk* OR score* OR index* OR rule* OR algorithm* OR model* OR measure*))
19	TS= ((multiple OR concurrent*) near/1 (disease* OR condition* OR illness* OR diagnos* OR morbid*) near/2 (predict* OR risk* OR score* OR index* OR rule* OR algorithm* OR model* OR measure*))
20	TS= ((multipatholog* OR multi near/0 patholog*) near/2 (predict* OR risk* OR score* OR index* OR rule* OR algorithm* OR model* OR measure*))
21	TS=Elixhauser
22	TS=Charlson

Appendix Table 3.2: Inclusion and exclusion criteria for including studies in the review.

Area	Inclusion criteria	exclusion criteria
Language	No restrictions	If no translators are available for the non-English articles or letters
Study design	RCTs Cohort Case-control	Non-human studies case reports (single case report) study design papers case series cross sectional
Publication type	Systematic reviews (at least one database used) Non-systematic reviews Conference abstracts (2017 onwards only) Research letters	General letters commentaries
Population of interest	The population or a defined subpopulation have AMI or ACS (clinically diagnosed STEMI or NSTEMI or UA)	Patients with stable angina or mixed CV disease diagnoses should be excluded.
Outcome of interest	Mortality. Major adverse cardiac and cerebrovascular events (MACCE). Bleeding. (All are with no restriction on time point of outcome measurement (in-hospital, 30 days, 6 months, 1-year, etc.).	Does not include information on outcomes of interest including, mortality, MACCE, bleeding
Prognostic factors	The article includes at least one comorbidity measure/score/index. The article investigates the prognostic impact of comorbid burden with ACS outcomes using a comorbidity measure. The article reports the association between comorbid burden/comorbidity score/measure/index and at least one of the above outcomes.	If, the report used comorbidity scores/measures/indices, but did not report any association between comorbid burden and ACS outcomes. If, the report studied other prognostic factors, but only used comorbidity measure as a confounder rather than measuring and reporting the prognostic impact of comorbid burden using the comorbidity measure.

RCTs: Random clinical trials; AMI: acute myocardial infarction; MI: myocardial infarction; NSTEACS: non-ST-segment elevation myocardial infarction; STEMI: ST-elevation myocardial infarction; NA: not available; NSTEMI: non-ST-elevation myocardial infarction; ACS: acute coronary syndrome; MACCE: major acute cardiovascular and cerebrovascular events: composite of death, cardiac complications, stroke, and vascular complications.

Appendix Table 3.3: Summary of comorbidity measures or risk scores used in the identified studies.

Comorbidity measures	Background	Included comorbidity conditions or risk factors or parameters (weights or death-specific score or hazard ratio)
CCI	The CCI is a scoring system that developed weights for each condition based on the adjusted relative risk (RR) of one-year mortality and has been broadly validated for other groups of patients such as chronic ischaemic heart disease patients. It was developed by Mary Charlson and colleagues in 1987, which originally consisted of 19 conditions.	Myocardial infarction (1); Congestive heart failure (1); Peripheral vascular disease (1); Cerebrovascular disease (1); Dementia (1); Chronic pulmonary disease (1); Connective tissue disease (1); Ulcer disease (1); Mild liver disease (1); Diabetes (1); Hemiplegia (2); Moderate or severe renal disease (2); Diabetes with end organ damage (2); Any tumor (2); Leukemia (2); Lymphoma (2); Moderate or severe liver disease (3) Metastatic solid tumor (6); AIDS (6)
SAMI	The SAMI risk score comprises 11 parameters derived from a variety of traditional cardiovascular and non-cardiovascular comorbidities; every parameter corresponds to a weight which was based on its association with one-year mortality.	Age, 65-75 (2); Age, >75 (4); Results of echocardiography (4); No results of echocardiography study (2); Plasma sodium <135 mEq/L (2); Intervention for AMI, CABG (-6); Intervention for AMI, TT or/and PCI (-3); Renal disease (2); Anemia (2); Obesity (-2); disease including Gastro-intestinal haemorrhage, COPD, Malignant neoplasm, Alcohol or drug addition, Schizophrenia or psychosis, Neurological disorders (3)
SCM	The SCM consists of six conditions derived from CCI and is for older people.	Renal failure (2.14*); Severe anemia (1.99*); Diabetes (1.55*); Cerebrovascular disease (1.6*); Peripheral artery disease (1.81*); Chronic lung disease (1.96*)
CS	The CS contains 14 chronic diseases that were assigned a disease-specific score based on the strength of their impact on one-year mortality.	Chronic heart failure (4.336); Cancer, onset ≤5 year (2.954); Cancer, onset >5 year (0.256); Stroke (2.900); Peripheral artery disease (2.850); Angina, onset >1 month (2.540); Angina, onset ≤1 month (0.829); Diabetes (1.985); CABG (1.973); Depression (1.699); Previous MI (1.697); Cardiac arrhythmias (1.542); COPD (1.280); Renal failure (0.829)

SCI	The SCI was created using five comorbidity variables that were independently associated with the one-year mortality by assigning scores according to the weight of their hazard ratios.	Previous MI (1); Previous heart failure (2); Peripheral artery disease (2); Dementia (2); Mild renal failure (1); Severe renal failure (2)
CCI/Deyo	The original CCI was modified into 17 categories in 1992 by Deyo et al.	Myocardial infarct (1); Congestive heart failure (1); Peripheral vascular disease (1); Cerebrovascular disease (1); Dementia (1); Chronic pulmonary disease (1); Connective tissue disease (1); Ulcer disease (1); Mild liver disease (1); Diabetes (1); Hemiplegia (2); Moderate or severe renal disease (2); Diabetes with end organ damage (2); Any malignancy, including Leukemia, Lymphoma (2); Moderate or severe liver disease (3) Metastatic solid tumor (6); AIDS (6)
ECS/ van Walraven (Updated)	A modification of the Elixhauser comorbidity measures was developed by Van Walraven et al. in 2009.	Congestive heart failure (7); Valvular disease (-1); Pulmonary circulation Disorders (4); Peripheral vascular disorders (2); Hypertension (0); Paralysis (7); Other neurological disorders (6); Chronic pulmonary disease (3); Diabetes uncomplicated (0); Diabetes with chronic complications (0); Hypothyroidism (0); Renal failure (5); Liver disease (11); Peptic ulcer disease excluding bleeding (0); AIDS/HIV (0); Lymphoma (9); Metastatic cancer (12); Solid tumor without metastasis (4); Rheumatoid arthritis/collagen vascular diseases (0); Coagulopathy (3); Obesity (-4); Weight loss (6); Fluid and electrolyte disorders (5); Chronic Blood loss anemia (-2); Deficiency anemia (-2); Alcohol abuse (0); Drug abuse (-7); Psychoses (0); Depression (-3)

CCI: Charlson comorbidity index; SAMI: Soroka acute myocardial infarction; OR: odd ratio; SCM: simplified comorbidity measure; SCI: simple comorbidity index; CS: chronic comorbidity score; ECS: Elixhauser comorbidity scores; AIDS: acquired immunodeficiency syndrome; CABG: coronary artery bypass graft; TT: thrombolytic therapy; PCI: percutaneous coronary intervention; COPD: Chronic obstructive pulmonary disease; MI: Myocardial infarction; *: hazard ratio, the similar magnitude shows the equal weight on the included comorbidities.

Appendix Table 3.4: Summary of the studies performing model comparison.

Study ID	Study design; Year; Country	Study population size; type of population	Outcomes	Comorbidity measures used for model compared	prognostic factor/covariate; type of variable	If there are prognostic effect estimates or others; model performance measures used	Main Result
Gutacker 2015	Prospective cohort study; 2008-2009; Denmark, England, Slovenia, Spain and Portugal	144,687 AMI	In-patient mortality at 30 days	CCI/Deyo vs ECS	Individual comorbidities as binary variables in the model for both CCI and ECS.	No information about the association of comorbid burden with outcomes, no prognostic effect for comorbidity measures; Only C-statistic, calibration slope, AIC, Nagelkerke R^2 for model comparison	The ECS model significantly outperformed the CCI model in terms of model discrimination and goodness-of-fit. The differences in C-statistic, $R^2$and AIC were approximately 0.021, 0.024 and -1653, respectively, under internal or external validation.
Chu 2010	Retrospective cohort study; 2001-2002; Taiwan	8,961 AMI	In-hospital mortality 1-year mortality	CCI/Deyo vs CCI/Romano vs ECS	Individual comorbidities as binary variables in the model for all comorbidity measures	No information about the association of comorbid burden with outcomes, no prognostic effect for comorbidity measures; Only G^2-statistic, C-statistic for model comparison	Regardless of the outcomes or data period, the ECS model had the highest C-statistic (0.74-0.78); the CCI/Romano model had the second highest C-statistic (0.69-0.77); the CCI/Deyo had the lowest (0.68-0.76). All the above models had significant G^2-statistics (p-value < 0.0001) compared with the baseline model.

Study ID	Study design; Year; Country	Study population size; type of population	Outcomes	Comorbidity measures used for model compared	prognostic factor/covariate; type of variable	If there are prognostic effect estimates or others; model performance measures used	Main Result
Southern 2004	Retrospective cohort study; 1995-2001; Canada	4,833 AMI	In-hospital mortality	CCI/Deyo vs ECS	Individual comorbidities as binary variables in the model for both CCI and ECS.	No information about the association of comorbid burden with outcomes, no prognostic effect for comorbidity measures; Only change in -2LogL, C-statistic for model comparison	The ECS model outperformed the CCI model in predicting mortality, with higher C-statistic values (0.79 vs. 0.70).
Li 2010	N retrospective cohort study; 2005-2006; US	5,749 AMI as subgroup	in-hospital mortality 6-month mortality	CCI/Dartmouth-Manitoba vs ECS vs CMS-HCC	Summary scores (no report what type of variable); Individual comorbidities as binary variables for all measures	No information about the association of comorbid burden with outcomes, no prognostic effect for comorbidity measures; Only C-statistic, AIC, BIC for model comparison	Regardless of using summary scores or individual comorbidities in the model, the CMS-HCC model is preferred over the CCI and ECS methods if patient diagnoses prior to the index hospitalisation are available. The range of C-statistics: CMS-HCC vs CCI vs ECS (0.64-0.85, 0.62-0.65, 0.63-0.71, in predicting in-hospital mortality; 0.72-0.81, 0.69-0.73, 0.68-0.76 in predicting 6-month mortality.

Study ID	Study design; Year; Country	Study population size; type of population	Outcomes	Comorbidity measures used for model compared	prognostic factor/covariate; type of variable	If there are prognostic effect estimates or others; model performance measures used	Main Result
Stukenborg 2001	Retrospective cohort study; 1994-1997; US	45,646 AMI as subgroup	in-hospital mortality	CCI/Deyo vs ECS	Individual comorbidities as binary variables in the model for both CCI and ECS.	No information about the association of comorbid burden with outcomes, no prognostic effect for comorbidity measures; Only C-statistic for model comparison	The risk adjustment models that use the ECS to identify comorbid illnesses demonstrate statistical performance that is substantially higher than models using the CCI regardless of using the index or prior hospitalisation records (C-statistics: 0.72-0.78 vs 0.71-0.72).
Normand 1994	Retrospective cohort study; 1986-1989; US	TD: 162,299 AMI VD: 164,427 AMI in 1988 and 10,466 AMI from 1988-1991	2-year mortality	C_{ADM} vs C_{DISCH} vs CCI/Deyo	Individual comorbidities as binary variables in the model for all measures.	No information about the association of comorbid burden with outcomes, no prognostic effect for comorbidity measures; Only C-statistic for model comparison	The C_{DISCH} model had better predictive performance than the C_{ADM} model and the CCI/Deyo model (C-statistic: 0.73 vs 0.68 vs 0.66; 072 vs 0.67 vs 0.65 in two validation cohorts, respectively).

Study ID	Study design; Year; Country	Study population size; type of population	Outcomes	Comorbidity measures used for model compared	prognostic factor/covariate; type of variable	If there are prognostic effect estimates or others; model performance measures used	Main Result
Gili 2011	Retrospective cohort study; 2003-2009; Spain	5,275 AMI	In-hospital mortality	CCI/Deyo vs ECS vs Four specific comorbidities	Summary scores of CCI and ECS, then as continuous variable (number of comorbidities as scores for ECS); Individual comorbidities as binary variables for 4 Specific comorbidities	Logistic regression (OR for CCI and ECS, individual comorbidities); Only C-statistic for model comparison	The model with specific comorbidities showed the best predictive ability (C-statistics: 0.785), the model with CCI had the second rank (0.733) and the model with ECS had the lowest C-statistic (0.727).

Study ID	Study design; Year; Country	Study population size; type of population	Outcomes	Comorbidity measures used for model compared	prognostic factor/covariate; type of variable	If there are prognostic effect estimates or others; model performance measures used	Main Result
Grunau 2006	historical inception cohort study; from 1994 or 1995; Canada	4,874 AMI	All-cause mortality at 1, 2, 3, 4, and 5 years	CCI/D'Hoore vs OAMIPR vs Number of distinct comorbidities present	CCI as an ordinal variable with 5 groups, number of distinct comorbidities as a categorical variable with 4 levels; Individual comorbidities in OAMIPR as binary variables (no reported)	No information about the association of comorbid burden with outcomes, no prognostic effect for comorbidity measures; Only C-statistic, Nagelkerke R^2 for model comparison	The model with OAMIPR had the best predictive performance than the CCI model, with the highest C-statistic (0.74-0.8) in predicting mortality including all periods and almost the highest R^2 (0.19-0.27) in predicting mortality at 2, 3, 4 and 5 years.

Study ID	Study design; Year; Country	Study population size; type of population	Outcomes	Comorbidity measures used for model compared	prognostic factor/covariate; type of variable	If there are prognostic effect estimates or others; model performance measures used	Main Result
Erickson 2014	Retrospective cohort study; 1999-2007; US	1,202 ACS	Inpatient mortality; 6 to 12 months mortality	CCI/D'Hoore Vs GRPI Vs Combined CCI and GRPI into model as two variables	Summary scores as continuous variables for all measures	Logistic regression (OR for CCI and GRPI, combined CCI/GRPI); Only change in -2LogL, C-statistic, Hosmer-Lemeshow test statistic for model comparison	The model with a combination of CCI and GRPI had the highest C-statistic when predicting the inpatient mortality (0.75 vs 0.73 vs 0.68) and the 6-12-month mortality (0.81 vs 0.74 vs 0.77, respectively), compared to the CCI model or GRPI model.
Albertsen 2020 (Updated)	Retrospective cohort study; 2000-2013; Demark	TD: 36,685 AMI in Demark (2000-2013) VD: 75,069 AMI in New Zealand (2007-2016)	1-year all-cause mortality	CCI (original) vs ECS vs DANCAMI Vs rDANCAMI	Summary scores as continuous variables and categorical variables for all measures	No information about the association of comorbid burden with outcomes, no prognostic effect for comorbidity measures; Nagelkerke's , R^2, Harrell's C-statistic, the Integrated Discrimination Improvement.	Regardless of variable types, the DANCAMI model outperformed the ECS or CCI model in the Danish cohort and underperformed in the New Zealand cohort while the differences in the performance measure were minor (≈0.01 in C-statistic). The CCI model had a slightly higher C-statistic than the ECS model in the Danish cohort (≈0.74) and vice versa in the New Zealand cohort (≈0.77).

AMI: acute myocardial infarction; CCI: Charlson comorbidity index; ECS: Elixhauser comorbid score; AIC: Akaike information criterion; -2LogL: log likelihood multiplied by -2; ; CMS-HCC: the Centre for Medicare and Medicaid Services Hierarchical condition category; ; BIC: Bayesian information criterion; C_ADM : comorbidity index using clinical conditions present at the time of admission; C_(DISCH): comorbidity index using conditions present after the acute episode of care; OAMIPR: Ontario AMI prediction rule, consisted by 9 parameters; ACS: acute coronary syndrome; l GRPI: GRACE risk prediction index, consisted of 9 parameter; DANCAMI: DANish Comorbidity index for Acute Myocardial Infarction.

Appendix Table 5a: ICD-9-CM codes used for other conditions, procedures and complications.

Table 5.1A:

Other conditions:	
Smoking	V15.82, 305.1
Atrial Fibrillation	427.31
Long-term use of anticoagulants	V58.61
History of disease or procedure:	
Previous PCI	V45.82
Prior CABG	V45.81
Treatments/Procedural Characteristics	
PCI	00.66, 36.01, 36.02, 36.05, 36.06, 36.07, 36.34
Coronary Angiography	88.53, 88.54, 88.55, 88.56, 88.57, 37.22, 37.23
CABG	361*, 36.31, 36.32, 369* , 36.33
IABP use	37.61
Clinical outcomes/Complications:	
Cardiac complications	37.0, 423.0, 423.3, 414.12
Acute ischemic Stroke	433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 435.0-1, 435.8-9, 436
Vascular complications	998.2, 999.2, 447, 868.04, 999.7 39.31, 39.41, 39.49, 39.52, 39.53, 39.56 - 39.59 39.79
Major Bleeding	CSS153, 430, 431, 432.x, 568.81, 998.1x

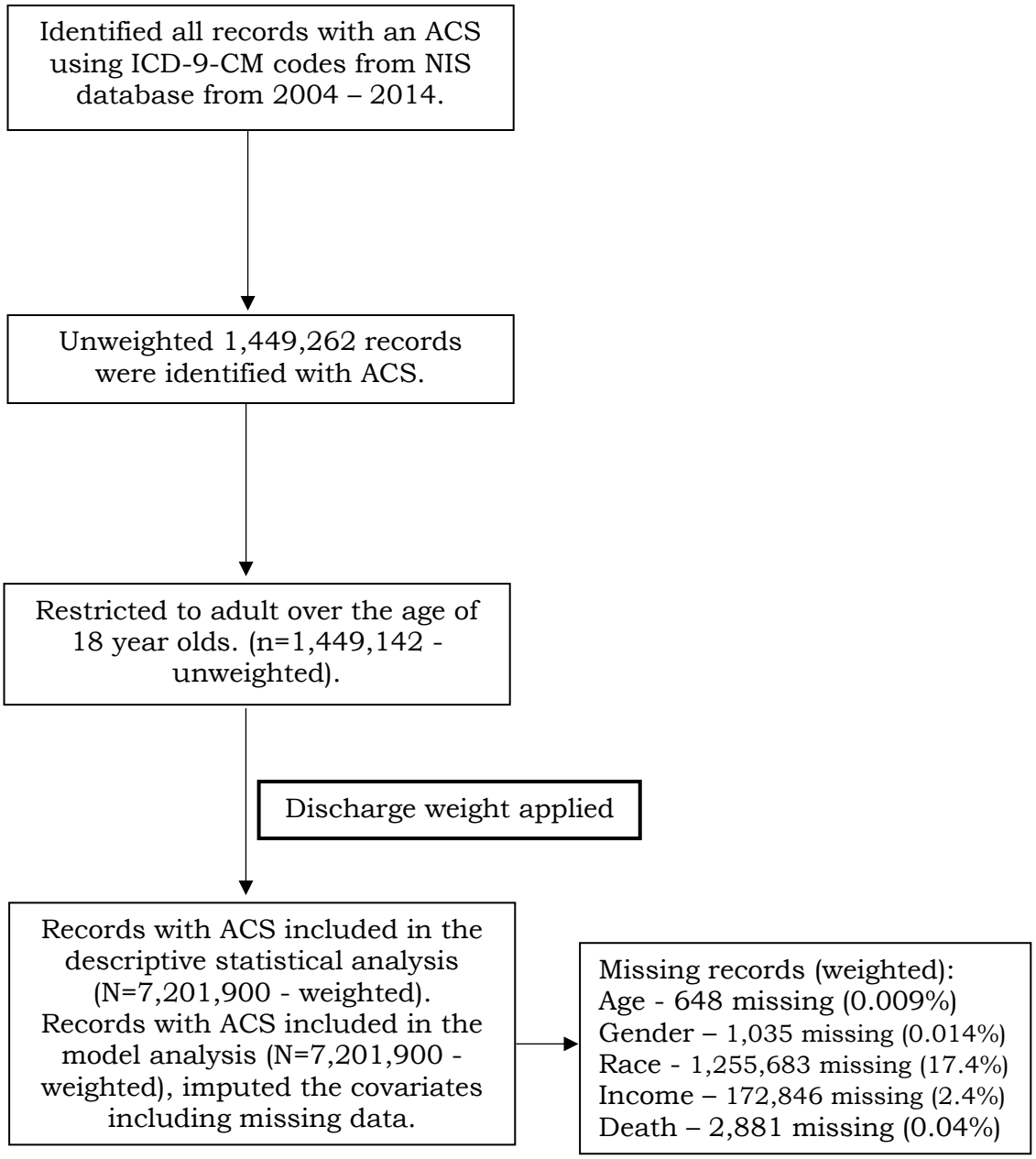
ICD-9-CM: International Classification of Diseases, Ninth Edition, Clinical Modification; CCS: Clinical Classification Software; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; IABP: intra-aortic balloon pump.

Appendix Table 5b: Deyo's modification of Charlson's comorbidity scoring system (CCI).

Table 5.1B:

412	Previous Myocardial infarction	1
428 – 428.9	Congestive heart failure	1
433.9, 441 – 441.9, 785.4 V43.4	Peripheral vascular disease	1
V1254, 438*	Previous Cerebrovascular disease	1
290 – 290.9	Dementia	1
490 – 496, 500 –505, 506.4	Chronic pulmonary disease	1
710.0, 710.1, 710.4, 714 – 714.2, 714.81, 725	Rheumatologic disease	1
531 – 534.9	Peptic ulcer	1
571.2, 571.5, 571.6, 571.4 –571.49	Mild liver disease	1
250 – 250.3, 250.7	Diabetes	1
250.4 – 250.6	Diabetes with chronic complications	2
344.1, 342 – 342.9	Hemiplegia or paraplegia	2
582 – 582.9, 583 – 583.7, 585, 586, 588 – 588.9	Renal Disease	2
140 – 172.9, 174 – 195.8, 200 – 208.9	Any malignancy including leukaemia and lymphoma	2
572.2 – 572.8	Moderate or severe liver disease	3
196 – 199.1	Metastatic solid tumour	6
042 – 044.9	AIDS	6

Appendix Figure 5.1: Flow diagram of included/excluded records.



Appendix Table 5.2: Impact of a 1-unit increase of CCI on the odds of clinical outcomes with ACS diagnosis (adjusted odds ratio, 95% confidence intervals §).

Outcomes	Increase of a 1-unit CCI score
MACCE	1.12 (1.11, 1.13)
In-hospital mortality	1.20 (1.19, 1.21)
Acute ischemic stroke	1.19 (1.18, 1.20)
Major Bleeding	1.12 (1.12, 1.13)

ACS: acute coronary syndrome; CCI: Charlson comorbidity index; MACCE: major acute cardiovascular and cerebrovascular events: composite of death, cardiac complications, stroke, and vascular complications.
§ Adjustment for age, gender, ethnicity, day of admission (weekday/weekend), median income, If the patient smokes, diagnosis of atrial fibrillation, long-term use of anticoagulants, previous procedure of percutaneous coronary intervention, previous procedure of coronary artery bypass graft, use of percutaneous coronary intervention, coronary angiography, coronary artery bypass graft, use of intra-aortic balloon pump, infusion of thrombolytic agent and year of hospitalisation.

Appendix Table 5.3: Association between individual Charlson component and clinical outcomes with ACS diagnosis (odds ratio, 95% confidence intervals §).

	In-hospital mortality and complications			
Individual Charlson component	**MACCE**	**Mortality**	**Acute ischemic stroke**	**Major Bleeding**
Previous Myocardial infarction	0.79 (0.77,0.81)	0.79 (0.76, 0.81)	1.01 (0.98,1.04)	0.92 (0.90,0.94)
Congestive heart failure	1.35 (1.32,1.37)	1.44 (1.41,1.46)	1.06 (1.04,1.09)	1.67 (1.64,1.71)
Peripheral vascular disease	1.42 (1.35,1.49)	1.36 (1.30,1.44)	1.70 (1.60,1.79)	1.34 (1.28,1.40)
Previous Cerebrovascular disease	1.16 (1.13,1.19)	1.05 (1.01,1.08)	2.26 (2.20,2.33)	1.02 (0.99,1.05)
Dementia	1.14 (1.07,1.21)	0.89 (0.83,0.96)	8.98 (8.25,9.78)	1.01 (0.93,1.08)
Chronic pulmonary disease	1.01 (0.99,1.01)	1.06 (1.04,1.08)	1.10 (1.07,1.12)	1.15 (1.13,1.17)
Rheumatologic disease	0.91 (0.86,0.95)	0.92 (0.87,0.97)	0.94 (0.88,1.01)	1.19 (1.14,1.23)
Peptic ulcer	0.92 (0.86,0.98)	0.82 (0.76,0.88)	1.17 (1.08,1.27)	8.24 (7.85,8.64)
Mild liver disease	1.25 (1.14,1.38)	1.40 (1.26,1.56)	0.90 (0.78,1.04)	2.47 (2.30,2.65)
Diabetes	0.88 (0.86, 0.89)	0.91 (0.89,0.93)	1.10 (1.07,1.12)	1.03 (1.02,1.04)

	In-hospital mortality and complications			
Individual Charlson component	**MACCE**	**Mortality**	**Acute ischemic stroke**	**Major Bleeding**
Diabetes with chronic complications	0.92 (0.89, 0.95)	0.91 (0.87,0.95)	1.44 (1.39,1.50)	1.72 (1.67,1.77)
Hemiplegia or paraplegia	23.8 (22.3,25.5)	2.12 (1.94,2.31)	50.6 (50.1,51.4)	1.87 (1.73,2.01)
Renal Disease	1.74 (1.65, 1.83)	1.93 (1.83,2.04)	1.10 (1.02,1.19)	1.89 (1.80, 1.96)
Any malignancy including leukaemia and lymphoma	1.27 (1.23, 1.32)	1.36 (1.30,1.41)	0.98 (0.93,1.04)	1.96 (1.90,2.03)
Moderate or severe liver disease	3.42 (3.05, 3.84)	3.99 (1.30,1.41)	1.43 (1.17,1.75)	2.81 (2.53, 3.13)
Metastatic solid tumour	1.78 (1.68, 1.89)	1.80 (1.69,1.92)	1.34 (1.22,1.47)	1.71 (1.62,1.81)
AIDS	1.30 (1.05, 1.60)	1.61 (1.26,2.06)	0.83 (0.57,1.21)	1.44 (1.23,1.70)

ACS: acute coronary syndrome.

§ Adjustment for age, gender, ethnicity, day of admission (weekday/weekend), median income, If the patient smokes, diagnosis of atrial fibrillation, long-term use of anticoagulants, previous procedure of percutaneous coronary intervention, previous procedure of coronary artery bypass graft, use of percutaneous coronary intervention, coronary angiography, coronary artery bypass graft, use of intra-aortic balloon pump, infusion of thrombolytic agent and year of hospitalisation.

Appendix Table 6.1: van Walraven Elixhauser comorbidity weighting scoring system.

Elixhauser comorbidity	**Points**
Congestive heart failure	7
Valvular disease	-1
Pulmonary circulation Disorders	4
Peripheral vascular disorders	2
Hypertension (combine uncomplicated and complicated)	0
Paralysis	7
Other neurological disorders	6
Chronic pulmonary disease	3
Diabetes uncomplicated	0
Diabetes with chronic complications	0
Hypothyroidism	0
Renal failure	5
Liver disease	11
Peptic ulcer disease excluding bleeding	0
AIDS/HIV	0
Lymphoma	9
Metastatic cancer	12
Solid tumor without metastasis	4
Rheumatoid arthritis / collagen vascular diseases	0
Coagulopathy	3
Obesity	-4
Weight loss	6
Fluid and electrolyte disorders	5
Chronic Blood loss anemia	-2
Deficiency anemia	-2
Alcohol abuse	0
Drug abuse	-7
Psychoses	0
Depression	-3

Appendix Table 6.2: Secular trends of baseline characteristics between 2004 and 2014 in ACS patients (7,201,900).

Variable	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Missing
Elixhauser Comorbidities, %												
Congestive heart failure	1.0%	0.9%	0.8%	0.7%	0.9%	1.0%	0.9%	0.9%	0.7%	0.7%	0.7%	None
Valvular disease	0.3%	0.3%	0.3%	0.2%	0.2%	0.2%	0.2%	0.3%	0.2%	0.2%	0.2%	None
Pulmonary circulation Disorders	0.04%	0.04%	0.04%	0.06%	0.1%	0.1%	0.2%	0.2%	0.1%	0.1%	0.1%	None
Peripheral vascular disorders	8.2%	8.2%	8.9%	10.0%	10.6%	11.1%	11.0%	12.1%	12.0%	12.1%	12.4%	None
Hypertension (combine uncomplicated and complicated)	57.4%	59.0%	61.4%	63.2%	65.7%	67.7%	69.1%	70.8%	72.0%	73.3%	74.0%	None
Paralysis	1.5%	1.4%	1.4%	1.5%	1.9%	1.6%	1.6%	1.7%	1.6%	1.6%	1.6%	None
Other neurologic disorder	4.6%	4.9%	5.0%	5.5%	6.0%	6.0%	5.8%	6.3%	6.1%	6.2%	6.2%	None
Chronic pulmonary disease	19.5%	20.6%	20.3%	20.7%	20.1%	20.1%	20.0%	21.0%	21.1%	21.2%	21.4%	None
Diabetes uncomplicated	25.2%	25.2%	26.0%	26.9%	27.5%	28.1%	28.7%	29.6%	30.5%	30.8%	31.1%	None
Diabetes with chronic complications	4.6%	4.8%	4.7%	5.4%	5.6%	5.7%	6.0%	6.8%	6.8%	7.1%	7.5%	None
Hypothyroidism	7.3%	7.7%	7.9%	8.7%	9.5%	9.9%	10.1%	11.0%	11.3%	11.4%	11.8%	None

Variable	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Missing
Renal failure	7.4%	9.2%	13.7%	15.8%	15.9%	17.0%	18.1%	19.9%	19.5%	20.3%	20.7%	None
Liver disease	0.8%	0.8%	0.9%	1.0%	1.0%	1.1%	1.2%	1.4%	1.5%	1.5%	1.7%	None
Peptic ulcer disease excluding bleeding	0.06%	0.04%	0.04%	0.04%	0.03%	0.03%	0.03%	0.04%	0.02%	0.02%	0.03%	None
AIDS/HIV	0.1%	0.1%	0.1%	0.1%	0.1%	0.2%	0.2%	0.2%	0.1%	0.1%	0.1%	None
Lymphoma	0.4%	0.4%	0.4%	0.4%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	None
Metastatic cancer	0.7%	0.8%	0.8%	0.9%	0.9%	0.9%	0.9%	0.9%	0.8%	0.8%	0.9%	None
Solid tumor without metastasis	1.3%	1.3%	1.3%	1.4%	1.5%	1.4%	1.4%	1.5%	1.4%	1.5%	1.4%	None
Rheumatoid arthritis/collagen vascular diseases	1.7%	1.8%	1.9%	2.0%	2.1%	2.1%	2.3%	2.4%	2.5%	2.4%	2.5%	None
Coagulopathy	2.9%	3.0%	3.1%	3.5%	3.5%	4.1%	4.4%	5.1%	5.2%	5.4%	5.5%	None
Obesity	7.4%	8.0%	8.3%	9.6%	11.0%	12.3%	12.2%	14.0%	15.1%	16.1%	17.1%	None
Weight loss	1.1%	1.2%	1.3%	1.5%	2.0%	2.2%	2.3%	2.9%	2.7%	2.8%	2.7%	None
Fluid and electrolyte disorders	14.3%	15.4%	15.8%	16.9%	18.3%	18.6%	19.1%	20.9%	21.1%	21.9%	22.6%	None
Chronic Blood loss anemia	1.3%	1.4%	1.3%	1.4%	1.1%	1.0%	0.9%	0.9%	0.8%	0.7%	0.7%	None
Deficiency	10.2%	10.5%	11.2%	13.4%	14.8%	15.4%	15.7%	17.4%	16.5%	16.2%	16.3%	None

Variable	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Missing
anemias												
Alcohol abuse	2.2%	2.3%	2.6%	2.6%	2.7%	2.8%	3.0%	3.0%	3.2%	3.3%	3.3%	None
Drug abuse	1.3%	1.5%	1.8%	1.9%	1.7%	2.0%	2.1%	2.3%	2.4%	2.6%	2.9%	None
Psychoses	1.4%	1.4%	1.5%	1.7%	2.1%	2.1%	2.3%	2.5%	2.5%	2.7%	2.7%	None
Depression	4.4%	4.7%	5.2%	5.7%	6.3%	6.6%	7.0%	7.6%	7.8%	8.0%	8.3%	None
Elixhauser Comorbidity Index Score, %												
0 (ECS <0)	12.8%	13.2%	13.2%	13.9%	14.2%	15.0%	14.9%	15.3%	15.9%	16.1%	16.6%	None
1 (ESC=0)	45.6%	43.4%	41.6%	38.7%	37.7%	36.4%	36.3%	33.8%	33.6%	32.8%	31.6%	None
2 (ESC=1-5)	26.2%	26.8%	27.0%	27.6%	27.4%	27.3%	27.3%	27.5%	27.6%	27.6%	28.0%	None
3 (ESC=6-13)	13.1%	14.3%	15.6%	16.7%	17.3%	17.6%	17.7%	19.1%	18.6%	19.2%	19.2%	None
4 (ESC≥14)	2.1%	2.4%	2.6%	3.1%	3.5%	3.7%	3.8%	4.4%	4.3%	4.3%	4.6%	None
Number of Elixhauser Comorbidities, %												
0 (NEC=0)	15%	14%	13%	11%	11%	10%	10%	9%	8%	8%	7%	None
1 (NEC=1)	28%	27%	26%	24%	23%	22%	22%	20%	20%	19%	19%	None
2 (NEC=2)	27%	28%	27%	26%	25%	25%	25%	23%	23%	23%	23%	None
3 (NEC=3)	17%	18%	18%	19%	19%	19%	19%	20%	20%	20%	20%	None
4 (NEC=4)	8%	9%	10%	11%	11%	12%	12%	13%	14%	14%	14%	None
5 (NEC≥5)	4%	5%	6%	8%	10%	11%	12%	15%	15%	16%	16%	None

ACS: acute coronary syndrome; IQR: interquartile range; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; ECS: Elixhauser comorbidity Index score; NEC: number of Elixhauser comorbidities; IABP: intra-aortic balloon pump; MI: myocardial infarction.

Appendix Table 6.3: Association between individual Elixhauser component and in-hospital clinical outcomes with acute coronary syndrome diagnosis (odds ratio and 95% confidence intervals), adjusted for potential confounders.§

	Outcomes			
Individual Elixhauser component	**MACCE**	**Mortality**	**Acute ischemic stroke**	**Major Bleeding**
Congestive heart failure	2.13 (2.02,2.25)	1.51 (1.41, 1.62)	1.32 (1.21, 1.44)	1.92 (1.80, 2.05)
Valvular disease	1.13 (1.03,1,24)	1.10 (0.98, 1.25)	1.14 (0.99, 1.30)	0.97 (0.86, 1.09)
Pulmonary circulation Disorders	1.06 (0.92,1.22)	1.17 (0.97, 1.41)	1.06 (0.87, 1.29)	1.33 (1.13, 1.58)
Peripheral vascular disorders	1.61 (1.58,1.64)	1.27 (1.23, 1.30)	2.44 (2.38, 2.50)	1.31 (1.29, 1.34)
Hypertension (combine uncomplicated and complicated)	0.72 (0.71,0.73)	0.64 (0.63, 0.65)	1.07 (1.05, 1.09)	0.87 (0.86, 0.89)
Paralysis	2.99 (2.87,3.10)	1.42 (1.34, 1.49)	7.08 (6.72, 7.45)	1.38 (1.32, 1.44)
Other neurologic disorder	1.61 (1.57,1.64)	1.68 (1.63, 1.73)	1.80 (1.72, 1.85)	1.12 (1.09, 1.15)
Chronic pulmonary disease	1.04 (1.03,1.06)	1.07 (1.05, 1.09)	1.02 (1.00, 1.04)	1.14 (1.12, 1.16)
Diabetes uncomplicated	0.93 (0.91,0.94)	1.03 (1.01, 1.05)	1.08 (1.05, 1.10)	1.02 (1.00, 1.03)
Diabetes with chronic complications	0.91 (0.89,0.93)	0.91 (0.88, 0.95)	1.20 (1.17, 1.25)	1.25 (1.21, 1.28)
Hypothyroidism	0.84 (0.83,0.86)	0.80 (0.78, 0.82)	0.94 (0.92, 0.97)	0.93 (0.90, 0.95)
Renal failure	1.21 (1.19,1.23)	1.43 (1.40, 1.46)	1.08 (1.05, 1.11)	1.50 (1.47, 1.53)
Liver disease	1.08 (1.03,1.13)	1.51 (1.41, 1.61)	0.93 (0.85, 1.01)	1.73 (1.65, 1.82)
Peptic ulcer disease excluding bleeding	0.76 (0.56,1.02)	0.69 (0.43, 1.08)	1.14 (0.70, 1.83)	2.38 (1.84, 3.08)
AIDS/HIV	1.04 (0.90, 1.22)	1.43 (1.12, 1.84)	0.78 (0.54, 1.15)	1.16 (0.97, 1.37)

Individual Elixhauser component	Outcomes			
	MACCE	**Mortality**	**Acute ischemic stroke**	**Major Bleeding**
Lymphoma	0.99 (0.93,1.06)	1.12 (1.02, 1.23)	0.90 (0.80, 1.03)	1.92 (1.79, 2.06)
Metastatic cancer	1.55 (1.47,1.62)	2.02 (1.90, 2.14)	1.35 (1.24, 1.47)	2.17 (2.06, 2.29)
Solid tumor without metastasis	1.16 (1.11,1.20)	1.38 (1.31, 1.46)	1.07 (1.00, 1.14)	1.59 (1.53, 1.66)
Rheumatoid arthritis/collagen vascular diseases	0.91 (0.87,0.94)	0.97 (0.92, 1.02)	0.96 (0.90, 1.02)	1.10 (1.06, 1.15)
Coagulopathy	1.51 (1.47,1.55)	1.56 (1.51, 1.62)	1.13 (1.09, 1.18)	1.85 (1.79, 1.91)
Obesity	0.90 (0.88,0.92)	0.85 (0.82, 0.88)	0.89 (0.87, 0.92)	0.94 (0.92, 0.97)
Weight loss	1.51 (1.46,1.56)	1.19 (1.14, 1.24)	1.28 (1.22, 1.35)	1.54 (1.47, 1.61)
Fluid and electrolyte disorders	1.97 (1.94,2.00	2.25 (2.21, 2.30)	1.18 (1.15, 1.20)	1.55 (1.52, 1.58)
Chronic Blood loss anemia	0.97 (0.92,1.01)	0.65 (0.60, 0.69)	1.11 (1.03, 1.19)	18.74 (17.50, 20.07)
Deficiency anemia	0.93 (0.91,0.95)	0.74 (0.72, 0.76)	1.02 (0.99, 1.04)	3.13 (3.04, 3.23)
Alcohol abuse	1.26 (1.22, 1.30)	1.13 (1.07, 1.19)	1.30 (1.23, 1.38)	1.25 (1.20, 1.30)
Drug abuse	1.05 (1.00,1.09)	1.04 (0.96, 1.12)	0.99 (0.90, 1.07)	1.07 (1.02, 1.13)
Psychoses	0.96 (0.93,1.00)	0.76 (0.71, 0.81)	1.17 (1.10, 1.24)	1.00 (0.96, 1.06)
Depression	0.82 (0.80,0.84)	0.75 (0.72, 0.77)	0.97 (0.94, 1.01)	0.91 (0.89, 0.94)

§ Adjustment for age, gender, ethnicity, day of admission (weekday/weekend), median income, If the patient smokes, diagnosis of dementia, diagnosis of atrial fibrillation, long-term use of anticoagulants, previous diagnosis of myocardial infarction, previous procedure of percutaneous coronary intervention, previous procedure of coronary artery bypass graft, use of percutaneous coronary intervention, coronary angiography, coronary artery bypass graft, use of intra-aortic balloon pump, infusion of thrombolytic agent and year of hospitalisation.

Appendix Table 6.4: Impact of a 1-unit increase of ESC on the odds of in-hospital clinical outcomes with ACS diagnosis (adjusted odds ratio, 95% confidence intervals §).

Outcomes	Increase of a 1-unit ECS	Increase of a 1-unit NEC
MACCE	1.087 (1.085, 1.088)	1.13 (1.12,1.14)
Mortality	1.084 (1.082, 1.086)	1.10 (1.09, 1.11)
Acute ischemic stroke	1.104 (1.101, 1.106)	1.20 (1.19, 1.21)
Major Bleeding	1.059 (1.057, 1.062)	1.18 (1.17, 1.19)

ACS: acute coronary syndrome; ECS: Elixhauser comorbidity Index score; NEC: number of Elixhauser comorbidities; MACCE: major acute cardiovascular and cerebrovascular events: composite of death, cardiac complications, stroke, and vascular complications.
§ Adjustment for age, gender, ethnicity, day of admission (weekday/weekend), median income, If the patient smokes, diagnosis of dementia, diagnosis of atrial fibrillation, long-term use of anticoagulants, previous diagnosis of myocardial infarction, previous procedure of percutaneous coronary intervention, previous procedure of coronary artery bypass graft, use of percutaneous coronary intervention, coronary angiography, coronary artery bypass graft, use of intra-aortic balloon pump, infusion of thrombolytic agent and year of hospitalisation.

Appendix Table 7.1a: AIC and BIC for Model goodness-of-fit from the second comparison way for DIED.

DIED	AIC								BIC							
	Model 4		5		6		7		Model 4		5		6		7	
	AIC_cci.cate		AIC_cci.cont		AIC_ecs.cate		AIC_ecs.cont		BIC_cci.cate		BIC_cci.cont		BIC_ecs.cate		BIC_ecs.cont	
1	523970.8	>	523778.8	>	512179.8	>	512100.1		524376.5	>	524160.3	>	512600.7	>	512484.9	
2	523975.5	>	523783.1	>	512183.4	>	512104		524381.1	>	524164.6	>	512604.3	>	512488.8	
3	523992.4	>	523799.6	>	512192.6	>	512109.8		524398	>	524181.1	>	512613.5	>	512494.6	
4	523983.2	>	523791.7	>	512191.5	>	512109.6		524389	>	524173.4	>	512612.6	>	512494.5	
5	523988.5	>	523795.5	>	512204.9	>	512124		524394.3	>	524177.2	>	512625.9	>	512509	
6	523975.9	>	523783.3	>	512184.1	>	512103.3		524381.6	>	524164.9	>	512605	>	512488.1	
7	523969.6	>	523776.8	>	512176.3	>	512095.4		524375.3	>	524158.5	>	512597.3	>	512480.3	
8	523926.9	>	523735.6	>	512139.5	>	512058.8		524332.7	>	524117.3	>	512560.5	>	512443.7	
9	523974	>	523782.4	>	512181.6	>	512100.3		524379.7	>	524164.1	>	512602.6	>	512485.3	
10	523946.7	>	523753.8	>	512153	>	512071.5		524352.4	>	524135.4	>	512573.9	>	512456.4	
11	523975.5	>	523782.9	>	512178.1	>	512098.7		524381.2	>	524164.6	>	512599.1	>	512483.7	
12	523949	>	523755.9	>	512163.3	>	512085.6		524354.8	>	524137.6	>	512584.3	>	512470.5	
13	523956.6	>	523764.5	>	512161.9	>	512080.1		524362.3	>	524146.2	>	512582.8	>	512465	

14	523976.9	>	523785.4	>	512180.2	>	512097.4		524382.5	>	524166.9	>	512601	>	512482.2
15	523971.3	>	523779.1	>	512181.9	>	512101.6		524377.2	>	524161	>	512603	>	512486.7
16	523950.2	>	523758.7	>	512159.2	>	512078.5		524356.1	>	524140.6	>	512580.4	>	512463.5
17	523965.2	>	523772.8	>	512182.4	>	512104.1		524370.8	>	524154.3	>	512603.3	>	512488.8
18	523965	>	523772.7	>	512176.4	>	512096.7		524370.8	>	524154.4	>	512597.4	>	512481.6
19	523973.4	>	523780.9	>	512190.4	>	512110.8		524379.1	>	524162.5	>	512611.3	>	512495.6
20	523960.6	>	523767.4	>	512166.6	>	512085.9		524366.5	>	524149.2	>	512587.7	>	512471

Appendix Table 7.1b: AIC and BIC for Model goodness-of-fit from the second comparison way for BLEEDING.

BLEEDING	AIC								BIC							
	Model 4		5		6		7		Model 4		5		6		7	
	AIC_cci.cate		AIC_cci.cont		AIC_ecs.cate		AIC_ecs.cont		BIC_cci.cate		BIC_cci.cont		BIC_ecs.cate		BIC_ecs.cont	
1	557365.1	>	557344.2	>	551598.2	<	553975.3		557746.5	>	557702.3	>	551993.1	<	554334.6	
2	557335.9	>	557314.4	>	551571.7	<	553948		557717.3	>	557672.6	>	551966.7	<	554307.4	
3	557350.2	>	557329	>	551585	<	553961.7		557731.1	>	557686.7	>	551979.4	<	554320.5	
4	557341.5	>	557320.7	>	551576	<	553954.3		557722.8	>	557678.7	>	551970.8	<	554313.5	
5	557348	>	557327.2	>	551584.4	<	553958.8		557729.3	>	557685.2	>	551979.2	<	554318	
6	557364.6	>	557343.8	>	551597.6	<	553975.4		557745.7	>	557701.7	>	551992.2	<	554334.5	
7	557350.4	>	557329.7	>	551585.7	<	553962.9		557731.6	>	557687.7	>	551980.4	<	554322	
8	557354.4	>	557333.6	>	551591.7	<	553965.9		557735.6	>	557691.6	>	551986.4	<	554325	
9	557358.4	>	557337	>	551590.6	<	553968.8		557739.6	>	557694.9	>	551985.3	<	554328	
10	557361.4	>	557340.3	>	551594.4	<	553971.4		557742.7	>	557698.3	>	551989.2	<	554330.7	
11	557334.1	>	557312.6	>	551569.9	<	553945.6		557715.3	>	557670.5	>	551964.6	<	554304.7	
12	557355.9	>	557333.8	>	551588.2	<	553965.5		557737.1	>	557691.8	>	551982.9	<	554324.6	
13	557375.3	>	557353.9	>	551607.4	<	553983.1		557756.4	>	557711.7	>	552001.9	<	554342	
14	557364.9	>	557344.1	>	551591.3	<	553973		557746.1	>	557702.1	>	551986	<	554332.1	
15	557391.1	>	557370.8	>	551619.8	<	553997.7		557772.3	>	557728.8	>	552014.5	<	554356.8	
16	557372.9	>	557351.7	>	551606	<	553982.2		557754.3	>	557709.9	>	552001	<	554341.6	

17	557351.8	>	557330.7	>	551587	<	553962.5		557733	>	557688.7	>	551981.7	<	554321.7
18	557371.8	>	557351.6	>	551607.4	<	553983.5		557753.2	>	557709.6	>	552002.2	<	554342.7
19	557350.7	>	557330	>	551589	<	553962.8		557731.9	>	557687.9	>	551983.7	<	554321.9
20	557353	>	557332.4	>	551592.5	<	553964.7		557734.3	>	557690.4	>	551987.4	<	554324

Appendix Table 7.1c: AIC and BIC for Model goodness-of-fit from the second comparison way for MACCE.

MACCE	AIC								BIC							
	Model 4		5		6		7		Model 4		5		6		7	
	AIC_cci.cate		AIC_cci.cont		AIC_ecs.cate		AIC_ecs.cont		BIC_cci.cate		BIC_cci.cont		BIC_ecs.cate		BIC_ecs.cont	
1	732771.7	>	732448	>	716632.6	>	715852.3		733165.8	>	732818.1	>	717043.7	>	716227.7	
2	732751.8	>	732428	>	716619.3	>	715838.7		733145.8	>	732798	>	717030.3	>	716214	
3	732769	>	732445	>	716628.5	>	715847.5		733163	>	732815.1	>	717039.5	>	716222.8	
4	732775.4	>	732452.5	>	716633.7	>	715851.7		733169.5	>	732822.7	>	717044.8	>	716227	
5	732759.8	>	732435.9	>	716624.1	>	715843.8		733153.9	>	732806.1	>	717035.2	>	716219.1	
6	732766.1	>	732442.2	>	716626.8	>	715846.1		733160.1	>	732812.3	>	717037.8	>	716221.3	
7	732764.4	>	732440.3	>	716626	>	715844.6		733158.3	>	732810.4	>	717036.9	>	716219.8	
8	732769.1	>	732446.1	>	716631.7	>	715851		733163	>	732816.2	>	717042.6	>	716226.2	
9	732782.4	>	732459.3	>	716640.2	>	715859.2		733176.5	>	732829.4	>	717051.3	>	716234.5	
10	732771.7	>	732447.5	>	716631.1	>	715850.9		733165.8	>	732817.8	>	717042.3	>	716226.3	
11	732767.6	>	732443.4	>	716627.8	>	715847.7		733161.7	>	732813.6	>	717039	>	716223.1	
12	732761.4	>	732437.1	>	716627.6	>	715848.8		733155.5	>	732807.3	>	717038.7	>	716224.1	
13	732767.4	>	732443.8	>	716627.4	>	715845.8		733161.4	>	732813.9	>	717038.5	>	716221.1	
14	732780.2	>	732458	>	716638.7	>	715856.8		733174.2	>	732828	>	717049.7	>	716232	
15	732767.6	>	732444.1	>	716628.3	>	715848.7		733161.8	>	732814.3	>	717039.4	>	716224.1	

16	732764.5	>	732441.1	>	716628.6	>	715849.2		733158.6	>	732811.3	>	717039.7	>	716224.6
17	732749.2	>	732425.4	>	716618.3	>	715838.4		733143.2	>	732795.5	>	717029.3	>	716213.7
18	732767.8	>	732444	>	716629.9	>	715849.5		733161.8	>	732814.2	>	717041	>	716224.9
19	732753.5	>	732430.1	>	716626.1	>	715846.5		733147.6	>	732800.3	>	717037.3	>	716221.9
20	732764.6	>	732440.6	>	716624.4	>	715843.9		733158.7	>	732810.8	>	717035.5	>	716219.3

Appendix Table 7.2a: Odds ratio (OR) with 95% confident internal (CI) for nonlinear terms from sensitivity analysis.

Model 9: Model 5 + CCI^2 + CCI^3				
DIED				
	OR	p-value	95% CI	
CCI	1.231325	0.000	1.20706	1.256077
CCI^2	0.9784524	0.000	.9726581	.9842813
CCI^3	1.001146	0.000	1.000707	1.001584
BLEEDING				
	OR	p-value	95% CI	
CCI	1.166486	0.000	1.138985	1.194651
CCI^2	0.9970926	0.460	.9894174	1.004827
CCI^3	0.9995032	0.115	.9988858	1.000121
MACCE				
	OR	p-value	95% CI	
CCI	1.176141	0.000	1.155585	1.197064
CCI^2	0.9945756	0.047	.9892405	.9999396
CCI^3	0.9998878	0.589	.9994802	1.000295
Model 11: Model 7 + ECS^2 + ECS^3				
DIED				
	OR	p-value	95% CI	
ECS	1.138519	0.000	1.132894	1.144172
ECS^2	0.9967743	0.000	.9961921	.9973568
ECS^3	1.000017	0.066	.9999989	1.000035
BLEEDING				
	OR	p-value	95% CI	
ECS	1.037139	0.000	1.033664	1.040625
ECS^2	1.003329	0.000	1.002872	1.003786
ECS^3	0.9998895	0.000	.9998727	.9999063
MACCE				
	OR	p-value	95% CI	
ECS	1.102883	0.000	1.098941	1.106839
ECS^2	1.000072	0.750	.9996287	1.000515
ECS^3	0.9999463	0.000	.9999318	.9999608

ECS: Elixhauser comorbidity score; CCI: Charlson comorbidity index; MACCE: major acute cardiovascular and cerebrovascular events: composite of death, cardiac complications, stroke, and vascular complications.

Appendix Table 7.2b: C-statistics with 95% confident internal (CI) from sensitivity analysis.

Models*	Different adverse Outcomes					
	Death		Bleeding		MACCE	
	C-statistic	95% CI	C-statistic	95% CI	C-statistic	95% CI
Model 5: Model 3 + continuous CCI.	0.8217	(0.8204, 0.8230)	0.6474	(0.6454, 0.6493)	0.7554	(0.7539, 0.7568)
Model 8: Model 5 + $\boldsymbol{CCI^2}$	0.8219	(0.8206, 0.8233)	0.6928	(0.6911, 0.6946)	0.8204	(0.8191, 0.8218)
Model 9: Model 5 + $\boldsymbol{CCI^2}$+ $\boldsymbol{CCI^3}$	0.8220	(0.8207, 0.8233)	0.6926	(0.6909, 0.6944)	0.8204	(0.8192, 0.8217)
Model 7: Model 3 + continuous ECS.	0.8373	(0.8360, 0.8385)	0.6593	(0.6573, 0.6612)	0.7755	(0.7741, 0.7769)
Model 10: Model 7 + $\boldsymbol{ECS^2}$	0.8379	(0.8367, 0.8392)	0.7059	(0.7044, 0.7074)	0.7758	(0.7744, 0.7772)
Model 11: Model 7 + $\boldsymbol{ECS^2}$ + $\boldsymbol{ECS^3}$	0.8379	(0.8367, 0.8392)	0.7058	(0.7043, 0.7074)	0.7759	(0.7746, 0.7773)

ECS: Elixhauser comorbidity score; CCI: Charlson comorbidity index; MACCE: major acute cardiovascular and cerebrovascular events: composite of death, cardiac complications, stroke, and vascular complications.
*95% CIs that crossed each other indicated there was not a statistically significant difference between the discrimination of the models being compared.

Appendix Table 7.2c: AIC and BIC for Model goodness-of-fit from sensitivity analysis.

Models*	Different adverse Outcomes					
	Death		Bleeding		MACCE	
	AIC	BIC	AIC	BIC	AIC	BIC
Model 5: Model 3 + continuous CCI.	523778.1	524159.7	557332.0	557690.0	732444.5	732814.6
Model 8: Model 5 + CCI^2	523668.3	524061.8	557189.9	557559.4	732302.9	732684.8
Model 9: Model 5 + CCI^2+ CCI^3	523643.3	524048.9	557189.2	557570.1	732304.8	732698.7
Model 7: Model 3 + continuous ECS.	512097.7	512482.6	553964.3	554323.4	715848.6	716223.9
Model 10: Model 7 + ECS^2	510954.8	511351.7	553948.5	554319.6	715333.1	715720.4
Model 11: Model 7 + ECS^2 + ECS^3	510952.9	511361.2	553693.5	554075.9	715261.2	715659.8

ECS: Elixhauser comorbidity score; CCI: Charlson comorbidity index; MACCE: major acute cardiovascular and cerebrovascular events: composite of death, cardiac complications, stroke, and vascular complications.
*A difference in AIC or BIC between models of < 2, 4-7, and >10 was interpreted as no, weak, and strong evidence of improved model fit, respectively.

Appendix Table 7.3: C-statistics with 95% confident internal (CI) from logistic regression models without interventions in predicting in-hospital outcomes.

Models*	Different adverse Outcomes					
	Death		Bleeding		MACCE	
	C-statistic	95% CI	C-statistic	95% CI	C-statistic	95% CI
Model 1: Patient's demographics.	0.6915	(0.6896, 0.6932)	0.5840	(0.5820, 0.5861)	0.6497	(0.6481, 0.6513)
Model 2: Model 1 + clinical risk factors.	0.7518	(0.7502, 0.7534)	0.6189	(0.6169, 0.6209)	0.7053	(0.7038, 0.7067)
Model 2-1: Model 2 + categorical CCI.	0.7636	(0.7621, 0.7651)	0.6266	(0.6246, 0.6285)	0.7160	(0.7145, 0.7175)
Model 2-2: Model 2 + continuous CCI.	0.7633	(0.7617, 0.7648)	0.6271	(0.6252, 0.6291)	0.7162	(0.7147, 0.7176)
Model 2-3: Model 2 + categorical ECS.	0.7921	(0.7906, 0.7935)	0.6417	(0.6401, 0.6436)	0.7474	(0.7459, 0.7487)
Model 2-3: Model 2 + continuous ECS.	0.7927	(0.7912, 0.7942)	0.6423	(0.6403, 0.6442)	0.7483	(0.7468, 0.7496)

ECS: Elixhauser comorbidity score; CCI: Charlson comorbidity index; MACCE: major acute cardiovascular and cerebrovascular events: composite of death, cardiac complications, stroke, and vascular complications.
*95% CIs that crossed each other indicated there was not a statistically significant difference between the discrimination of the models being compared.

Appendix Table 8: Summary statistics of baseline characteristics based on 16 combinations of ACS patients (7,201,900).

Subgroup	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12	S13	S14	S15	S16	Missing
	ECS≤0, CCI=0	ECS≤0, CCI=1	ECS ≤0, CCI =2	ECS ≤0, CCI≥ 3	ECS =1-5, CCI =0	ECS =1-5, CCI =1	ECS =1-5, CCI =2	ECS =1-5, CCI≥ 3	ECS =6-13, CCI =0	ECS =6-13, CCI =1	ECS =6-13, CCI =2	ECS =6-13, CCI≥ 3	ECS ≥14, CCI =0	ECS ≥14, CCI =1	ECS ≥14, CCI =2	ECS ≥14, CCI≥ 3	
Patient demographics																	
No. of weighted discharges with ACS	1,911,150	1,228,132	463,828	158,770	377,792	715,619	532,889	337,492	163,436	339,506	350,510	371,264	13,920	45,050	59,190	133,344	None
Median (IQR) age, y	59 (51-71)	64 (54-76)	68 (57-79)	68 (58-78)	68 (57-80)	71 (60-81)	72 (62-81)	72 (62-80)	75 (61-84)	76 (65-84)	76 (66-83)	74 (65-82)	75 (61-84)	75 (63-84)	76 (65-83)	74 (65-82)	648 (0.009 %)
Female, %	31.6 %	39.4 %	46.1 %	48.8 %	41.1 %	43.8 %	45.2 %	45.6 %	43.3 %	46.1 %	45.8 %	43.7 %	42.0%	44.4%	44.4%	40.7 %	1035 (0.014 %)
Race, %																	
White	78.9 %	74.0 %	73.3 %	73.4 %	77.9 %	78.4 %	76.7 %	74.3 %	78.5 %	77.0 %	76.2 %	73.5 %	70.3%	73.0%	74.2%	73.2 %	1,255,683 (17.4%)
black	7.9%	10.2 %	11.6 %	12.7 %	10.2 %	9.6 %	10.2 %	11.8 %	10.2 %	10.7 %	10.9 %	11.9 %	15.6%	13.2%	11.5%	12.6	
Hispanic	7.0%	9.1%	9.0 %	8.5 %	6.1 %	6.5 %	7.4 %	8.1 %	6.1 %	6.8 %	7.2 %	8.4 %	7.1 %	7.4 %	7.8 %	8.2 %	
Asian/Pacific islander	2.1%	2.3%	2.1 %	1.8 %	2.2 %	2.0 %	2.2 %	2.5 %	2.0 %	2.2 %	2.3 %	2.8 %	3.1 %	2.7 %	2.6 %	2.8 %	
Native American	0.5%	0.7%	0.7 %	0.7 %	0.6 %	0.5 %	0.7 %	0.6 %	0.4 %	0.5 %	0.6 %	0.6 %	0.6 %	0.5 %	0.5 %	0.6 %	
other	3.6%	3.8%	3.3 %	3.0 %	3.0 %	3.0 %	2.9 %	2.7 %	2.7 %	2.8 %	2.8 %	2.8 %	3.2 %	3.2 %	3.3 %	2.7 %	

Elixhasuer and Charlson Comorbidities, %																	
Subgroup	**S1**	**S2**	**S3**	**S4**	**S5**	**S6**	**S7**	**S8**	**S9**	**S10**	**S11**	**S12**	**S13**	**S14**	**S15**	**S16**	**Comorbidity index in which included**
	ECS≤ 0, CCI= 0	**ECS≤ 0, CCI= 1**	**ECS ≤0, CCI =2**	**ECS ≤0, CCI≥ 3**	**ECS =1-5, CCI =0**	**ECS =1-5, CCI =1**	**ECS =1-5, CCI =2**	**ECS =1-5, CCI≥ 3**	**ECS =6-13, CCI =0**	**ECS =6-13, CCI =1**	**ECS =6-13, CCI =2**	**ECS =6-13, CCI≥ 3**	**ECS ≥14, CCI =0**	**ECS ≥14, CCI =1**	**ECS ≥14, CCI =2**	**ECS ≥14, CCI≥ 3**	
Previous Myocardial infarction	NA	13.2 %	26.8 %	43.6 %	NA	4.9 %	15.1 %	31.6 %	NA	4.2 %	10.0 %	22.9 %	NA	1.9 %	5.9 %	14.7 %	CCI
Previous Cerebrovascular disease	NA	0.3%	0.8 %	1.7 %	NA	2.5 %	3.7 %	5.0 %	NA	1.9 %	3.1 %	4.8 %	NA	1.0 %	2.9 %	4.9 %	CCI
Dementia	NA	0.4%	1.3 %	2.6 %	NA	0.4 %	1.0 %	2.2 %	NA	0.6 %	1.2 %	2.2 %	NA	0.5 %	1.2 %	1.7 %	CCI
Mild liver disease	NA	0.00 24%	NA	0.01 5%	NA	0.03 2%	0.03 6%	0.08 8%	NA	0.8 %	1.0 %	1.4 %	NA	5.3 %	8.4 %	9.9 %	CCI
Moderate or severe liver disease	NA	NA	NA	2.0 %	NA	NA	NA	2.3 %	NA	NA	NA	1.0 %	NA	NA	NA	5.9 %	CCI
Congestive heart failure	NA	0.00 62%	0.0 %	0.02 5%	NA	0.2 %	0.2 %	0.2 %	NA	3.7 %	3.0 %	2.1 %	NA	14. 4%	13. 8%	8.2 %	CCI and ECS
Peripheral vascular disease	NA	2.2%	4.2 %	7.7 %	NA	16.9 %	18.6 %	21.8 %	NA	18.5 %	21.2 %	24.7 %	NA	18. 4%	24. 1%	26.2 %	CCI and ECS
Chronic pulmonary disease	NA	4.8%	13.9 %	28.9 %	NA	38.0 %	49.7 %	53.4 %	NA	28.9 %	49.4 %	55.0 %	NA	32. 1%	52. 8%	51.0 %	CCI and ECS
Rheumatologic/collagen vascular disease	NA	2.7%	4.9 %	7.3 %	NA	1.5 %	3.3 %%	5.7 %	NA	1.3 %	2.5 %	4.2 %	NA	0.8 %	2.1 %	3.0 %	CCI and ECS

Peptic ulcer	NA	0.05 %	0.08 %	0.15 %	NA	0.02 %	0.05 %	0.09 %	NA	0.02 %	0.05 %	0.06 %	NA	0.0 2%	0.0 7%	0.06 %	CCI and ECS
Diabetes, uncomplicated	NA	50.6 %	66.9 %	56.7 %	NA	23.4 %	45.0 %	50.4 %	NA	19.8 %	35.6 %	42.8 %	NA	13. 7%	26. 3%	34.1 %	CCI and ECS
Diabetes with chronic complications	NA	NA	8.6 %	29.7 %	NA	NA	7.2 %	27.7 %	NA	NA	7.2 %	26.4 %	NA	NA	6.2 %	18.0 %	CCI and ECS
Paralysis/hemiplegia	NA	NA	0.07 %	0.3 %	NA	NA	0.6 %	1.3 %	NA	NA	6.5 %	8.7 %	3.7 %	7.4 %	12. 7%	17.1 %	CCI and ECS
Moderate/severe renal disease	NA	NA	0.2 %	2.0 %	NA	NA	0.9 %	6.8 %	NA	NA	1.0 %	8.2 %	NA	NA	1.1 %	6.6 %	CCI
Renal Disease	0.2%	0.7%	2.0 %	6.3 %	19.6 %	19.6 %	22.7 %	31.7 %	28.4 %	38.8 %	45.3 %	53.1 %	54. 1%	53. 5%	55. 7%	53.6 %	ECS
Any malignancy including leukaemia and lymphoma	NA	NA	0.0 %	0.02 %	NA	NA	0.08 %	0.2 %	NA	NA	2.0 %	3.3 %	NA	NA	4.4 %	8.3 %	CCI and ECS
Metastatic cancer	NA	NA	NA	0.00 6%	NA	NA	NA	0.06 %	NA	NA	NA	6.0 %	NA	NA	NA	28.0 %	CCI and ECS
AIDS	NA	NA	NA	3.0 %	NA	NA	NA	0.7 %	NA	NA	NA	0.5 %	NA	NA	NA	0.6 %	CCI and ECS
Solid tumour without metastasis	NA	NA	NA	NA	0.01 %	0.01 %	2.8 %	6.6 %	0.03 %	0.04 %	2.3 %	10.4 %	0.1 %	0.1 %	2.5 %	8.7 %	ECS
Liver disease	0.00 3%	0.00 8%	0.00 6%	0.02 %	0.3 %	0.2 %	0.1 %	0.2 %	5.3 %	3.2 %	2.1 %	2.2 %	24. 1%	19. 6%	17. 4%	16.8 %	ECS

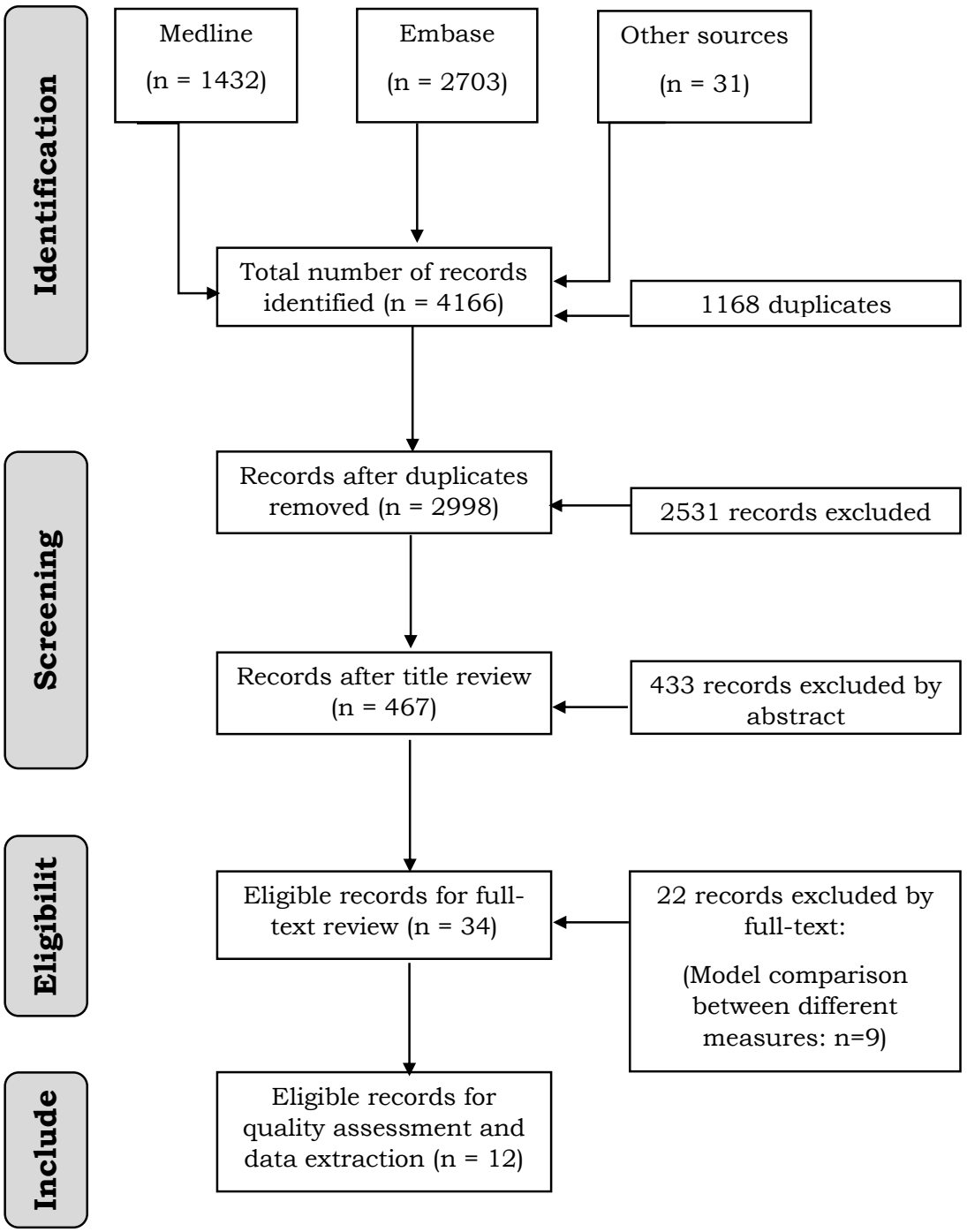
Hypertension	56.9 %	70.3 %	74.0 %	74.0 %	67.2 %	66.8 %	70.3 %	73.0 %	63.7 %	67.6 %	70.1 %	72.3 %	67.8%	65.9%	68.0%	68.0 %	ECS
Depression	5.1%	8.0%	12.3 %	19.8 %	5.4 %	4.4 %	5.4 %	7.9 %	3.3 %	4.2 %	4.9 %	6.2 %	3.3 %	3.5 %	3.7 %	4.9 %	ECS
Valvular disease	0.05 %	0.04 %	0.04 %	0.05 %	0.2 %	0.1 %	0.07 %	0.09 %	0.4 %	0.9 %	0.7 %	0.5 %	2.0 %	3.3 %	3.2 %	1.5 %	ECS
Pulmonary circulation disorders	0.00 1%	0.00 2%	0.00 1%	NA	0.08 %	0.02 %	0.02 %	0.00 6%	0.2 %	0.3 %	0.2 %	0.1 %	1.6 %	2.5 %	2.1 %	1.1 %	ECS
Neurodegenerative disorders	0.1%	0.2%	0.3 %	0.4 %	4.1 %	2.4 %	1.9 %	1.6 %	48.8 %	28.0 %	17.4 %	10.1 %	50.1%	42.6%	37.3%	23.6 %	ECS
Hypothyroidism	6.8%	8.8%	10.9 %	12.1 %	9.7 %	10.2 %	10.9 %	11.8 %	11.1 %	11.7 %	11.9 %	12.7 %	11.7%	11.0%	12.1%	11.6 %	ECS
Coagulopathy	0.3%	0.5%	0.7 %	0.9 %	8.6 %	4.7 %	3.2 %	2.5 %	14.2 %	13.3 %	10.6 %	8.2 %	33.6%	26.2%	21.5%	18.3 %	ECS
Obesity	10.2 %	18.0 %	25.4 %	37.6 %	6.8 %	6.9 %	9.1 %	15.0 %	3.0 %	3.9 %	5.1 %	8.8 %	1.6 %	2.4 %	2.9 %	4.3 %	ECS
Weight loss	0.02 %	0.03 %	0.06 %	0.09 %	0.6 %	0.5 %	0.4 %	0.4 %	9.1 %	7.8 %	5.4 %	3.5 %	41.3%	36.5%	29.4%	17.8 %	ECS
Fluid and electrolyte disorders	0.6%	1.0%	1.5 %	2.1 %	50.8 %	27.7 %	18.0 %	12.7 %	46.7 %	53.6 %	52.0 %	42.2.%	83.7%	77.8%	73.8%	60.3 %	ECS
Blood loss anemia	0.4%	0.8%	1.2 %	1.7 %	1.0 %	1.2 %	1.4 %	1.7 %	1.0 %	1.4 %	1.7 %	2.0 %	1.4 %	1.7 %	1.7 %	2.0 %	ECS
Deficiency anemia	4.9%	9.2%	15.3 %	23.1 %	13.5 %	14.7 %	18.7 %	26.8 %	13.6 %	18.8 %	24.2 %	32.6 %	25.0%	23.3%	24.6%	29.9 %	ECS
Alcohol abuse	2.9%	2.5%	2.2 %	2.2 %	3.3 %	2.8 %	2.3 %	1.7 %	3.7 %	3.5 %	3.0 %	2.1 %	7.6 %	7.3 %	6.7 %	4.7 %	ECS
Drug abuse	3.0%	3.2%	3.8 %	5.8 %	0.7 %	0.6 %	0.7 %	1.1 %	0.4 %	0.5 %	0.5 %	0.7 %	0.4 %	0.5 %	0.5 %	0.6 %	ECS

Psychosis	1.3%	1.8%	2.2 %	3.1 %	1.9 %	2.0 %	2.3 %	2.5 %	3.2 %	2.8 %	2.7 %	2.9 %	4.2 %	4.1 %	3.6 %	3.3 %	ECS
Treatments/procedural characteristics, %																	
PCI	57.4 %	47.2 %	36.3 %	30.4 %	43.5 %	37.9 %	31.0 %	25.8 %	32.6 %	26.1 %	23.2 %	21.7 %	20. 7%	19. 2%	19. 5%	17.3 %	None
CA	75.1 %	68.2 %	61.0 %	56.7 %	66.0 %	61.1 %	55.3 %	50.4 %	52.9 %	47.9 %	46.0 %	43.7 %	41. 4%	40. 0%	40. 2%	36.2 %	None
Infusion of thrombolytic agent	1.9%	1.5%	1.2 %	1.0 %	1.5 %	1.2 %	1.0 %	0.9 %	1.2 %	0.9 %	0.8 %	0.8 %	0.7 %	0.8 %	0.7 %	0.8 %	None
CABG	5.9%	8.0%	8.7 %	8.3 %	11.6 %	10.0 %	9.3 %	7.8 %	11.3 %	11.5 %	10.2 %	7.8 %	15. 3%	13. 8%	11. 8%	7.3 %	None
IABP use	3.1%	4.3%	4.6 %	3.8 %	6.1 %	5.4 %	4.9 %	3.9 %	6.7 %	7.0 %	5.9 %	4.2 %	9.9 %	9.1 %	7.9 %	4.9 %	None
Outcomes/complications, %																	
Mortality	1.9%	3.2%	3.9 %	3.6 %	6.7 %	6.3 %	6.1 %	5.8 %	11.5 %	11.9 %	11.1 %	9.5 %	15. 5%	17. 6%	15. 8%	15.1 %	2881 (0.04%)
Major Bleeding	3.1%	3.6%	4.0 %	4.5 %	6.1 %	5.3 %	5.0 %	5.3 %	7.1 %	7.2 %	7.0 %	6.6 %	10. 4%	9.6 %	11. 0%	9.2 %	None
MACCE	3.6%	5.0%	5.6 %	5.4 %	9.7 %	8.8 %	8.2 %	7.9 %	15.9 %	15.5 %	14.6 %	13.4 %	20. 7%	22. 4%	20. 7%	22.1 %	None

ACS: acute coronary syndrome; ECS: Elixhauser comorbidity scores; CCI: Charlson Comorbidity index; ACS: acute coronary syndrome; IQR: interquartile range; PCI: percutaneous coronary intervention; CA: coronary angiography; CABG: coronary artery bypass graft; IABP: intra-aortic balloon pump; MACCE: major acute cardiovascular and cerebrovascular events: composite of death, cardiac complications, stroke, and vascular complications.

APPENDIX II: UPDATED FIGURES AND TABLES IN CHAPTER 3

Updated Figure 3.1: Screening flowchart of articles for the systematic review.



Updated Table 3.1: Study design and characteristics of the included studies.

Study ID	Study design; Year; Country	Study population size; type of population	Age (median, mean ± SD, %)	Female (%)	Description of inclusion for participants
Schmidt 2012	Retrospective cohort study; 1984-2008; Denmark	234,331 AMI	Women: median 74 in 1984 to median 77 in 2008; Men: median 68	37.9%	All first-time hospitalisations for MI among Danish-born inhabitants aged 15 years or older.
Plakht 2010	Prospective cohort study; 2002-2004; Israel	1,885 AMI	<65, 44.6% 65-75, 26.3% >75, 29.1%;	31.6%	No age limitation. Patients who had been admitted with AMI and discharged alive from hospital.
Sanchis 2019	Prospective cohort study; 2002-2008 and 2010-2012; Spain	920 NSTEACS	76.4 ± 7.0	42%	Elderly (≥65) patients admitted for NSTEACS.
Balzi 2005	Prospective cohort study; 2000-2001; Italy	740 STEMI	69.5 ± 12.2	30.1%	No age limitation. All residents in the Florence area arriving alive to the emergency department of 1 of the 6 hospitals with a suspected STEMI.
Sanchis 2011	Prospective cohort study; 2002-2008, Spain	1017 NSTEACS	68 ± 13	34%	No age limitation. The patients who admitted to the Hospital with NSTEACS.

Núñez 2004	Prospective cohort study; 2000-2003; Spain	1035 AMI (508 STEMI, 527 NSTEMI)	68 ± 3	32.1%	No age limitation. Patients diagnosed with AMI who were admitted to hospital.
Ramirez-Marrero 2011	Prospective cohort study; 2004-2005; Spain	715 NSTEACS	66.2 ± 11.2	NA	No age limitation. Patients admitted to hospital for NSTEACS.
Radovanovic 2014	Prospective cohort study; 2002-2012; Swiss	29,620 ACS	66.3 ± 12.8	27%	No age limitation All ACS patients. ACS included acute MI and unstable angina.
Zhang 2020[a]	Retrospective cross-sectional study; 2004-2014; United State	6,613,623 ACS	67 (56-79)	40.0%	All adults (≥18 years) with the principal diagnosis of ACS.
Zhang 2020[b]	Retrospective cross-sectional study; 2004-2014; US	6,613,623 ACS	67 (56-79)	40.0%	All adults (≥18 years) with the principal diagnosis of ACS.
Pastor 2019	Prospective cohort study; no study period found; Spain	520 ACS	84.4 ± 3.6	38.5%	Elderly (≥80 years) patients hospitalised after NSTEACS.
Hautamäki 2020	Retrospect cohort study; 2015-2016; Finland	1576 ACS	69.3 ± 11.8	30.9%	Patients who underwent invasive evaluation by coronary angiography for a first episode of suspected ACS during a two-year period.

AMI: acute myocardial infarction; MI: myocardial infarction; NSTEACS: non-ST-segment elevation myocardial infarction; STEMI: ST-elevation myocardial infarction; NA: not available; NSTEMI: non-ST-elevation myocardial infarction; ACS: acute coronary syndrome.

Updated Figure 3.2: Risk of bias for the included studies according to the QUIPS tool.

	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Statistical Analysis and Reporting	Overall Risk of Bias
Schmidt 2012							
Plakht 2010							
Sanchis 2019							
Balzi 2005							
Sanchis 2011							
Núñez 2004							
RamirezMarrero 2011							
Radovanovic 2014							
Zhang 2020[a]							
Zhang 2020[b]							
Pastor 2019							
Hautamäki 2020							

Low risk (green); moderate risk (yellow); high risk (red).

Updated Table 3.2: Summary of measured outcome, comorbid measures used, modelling used, association presented and effect characteristics.

Study ID	Outcomes	Comorbidity measure used	prognostic factor/covariate; type of variable	Modelling	Final prognostic effect estimates for comorbidity measure (unadjusted and adjusted by other covariates)
Schmidt 2012	30-day all-cause mortality, 31-365 days all-cause mortality	The original CCI (19 conditions)	CCI as prognostic factor. Summary scores as a categorical variable (0, 1, 2, ≥3)	Cox proportional hazard regression	<u>30-day mortality:</u> Results from unadjusted models: 1 vs 0: HR=1.85 (95%CI: 1.73-1.98) 2 vs 0: HR=2.09 (95%CI: 1.94-2.25) ≥3 vs 0: HR=2.72 (95%CI: 2.53-2.91) Results from adjusted models: 1 vs 0: HR=1.35 (95%CI: 1.26-1.45) 2 vs 0: HR=1.52 (95%CI: 1.41-1.64) ≥3 vs 0: HR=1.96 (95%CI: 1.83-2.11) <u>31-365-day mortality:</u> Results from unadjusted models: 1 vs 0: HR=2.64 (95%CI: 2.42-2.87) 2 vs 0: HR=3.61 (95%CI: 3.30-3.96) ≥3 vs 0: HR=5.80 (95%CI: 5.34-6.31) Results from adjusted models: 1 vs 0: HR=1.83 (95%CI: 1.68-2.00) 2 vs 0: HR=2.50 (95%CI: 2.29-2.74) ≥3 vs 0: HR=3.89 (95%CI: 3.58-4.24)

Study ID	Outcomes	Comorbidity measure used	prognostic factor/covariate; type of variable	Modelling	Final prognostic effect estimates for comorbidity measure (unadjusted and adjusted by other covariates)
Plakht 2010	1-year all-cause mortality	SAMI (11 parameters)	SAMI as prognostic factor. Summary scores as a continuous variable	Logistic regression	Results from adjusted models: OR=1.39 (95%CI: 1.33-1.45)
Sanchis 2019	1-year all-cause mortality	SCM (6 comorbidities)	SCM as prognostic factor. Summary numbers of comorbidities as a categorical variable (0-1, 2, ≥3)	Cox proportional hazard regression	No results from unadjusted models. Results from adjusted models: 2 vs 0-1: HR=1.29 (95%CI: 0.81-2.04) ≥3 vs 0-1: HR=1.91 (95%CI: 1.20-3.03)
Balzi 2005	1-year all-cause mortality	CS (14 chronic diseases)	CS as a covariate. Summary scores and tertile to 3 categories (cut-off values can vary)	Cox proportional hazard regression	No results from unadjusted models. Results from adjusted models: 2 vs 1: HR=1.87 (95%CI: 1.04-3.38) 3 vs 1: HR=2.12 (95%CI: 1.18-3.82)
Sanchis 2011	1-year all-cause mortality	SCI (5 comorbidities)	SCI as prognostic factor. Summary points as a categorical variable (0, 1-2, ≥3)	Cox proportional hazard regression	No results from unadjusted models. Results from adjusted models: 1-2 vs 0: HR=1.7 (95%CI: 1.0-3.1) ≥3 vs 0: HR=4.8 (95%CI: 2.7-8.5)
Núñez 2004	30-day mortality or reinfarction, 1-year mortality or reinfarction	CCI/Deyo (17 comorbidities)	CCI as prognostic factor. Summary scores as a categorical variable (0,1,2, ≥3)	Cox proportional hazard regression	<u>30-day mortality or reinfarction:</u> No results from unadjusted models. Results from adjusted models: 1 vs 0: HR=1.69 (95%CI: 1.10-2.59) 2 vs 0: HR=1.78 (95%CI: 1.08-2.92)

Study ID	Outcomes	Comorbidity measure used	prognostic factor/covariate; type of variable	Modelling	Final prognostic effect estimates for comorbidity measure (unadjusted and adjusted by other covariates)
					≥3 vs 0: HR=1.57 (95%CI: 0.87-2.83) 1-year mortality or reinfarction: No results from unadjusted models. Results from adjusted models: 1 vs 0: HR=1.62 (95%CI: 1.18-2.23) 2 vs 0: HR=2.00 (95%CI: 1.39-2.89) ≥3 vs 0: HR=2.24 (95%CI: 1.50-3.36)
Ramirez-Marrero 2011	Intrahospital-phase mortality, Long-term (24-month) mortality, readmission for HF after follow-up, MACEs during follow-up	CCI (unknown version)	CCI as prognostic factor. Summary scores as a continuous variable	NA	Unclear whether the results are from unadjusted or adjusted models: Intrahospital- phase mortality: OR=1.6 (95%CI: 1.4-1.8) Long-term (24-month) mortality: OR=1.3 (95%CI: 1.2-1.5) readmission for HF: OR=1.2 (95%CI: 1.04-1.3) MACESs during follow-up: OR=1.1 (95%CI: 1-1.2)

Study ID	Outcomes	Comorbidity measure used	prognostic factor/covariate; type of variable	Modelling	Final prognostic effect estimates for comorbidity measure (unadjusted and adjusted by other covariates)
Radovanovic 2014	In-hospital mortality, 1-year mortality	The original CCI (19 conditions)	CCI as prognostic factor. For in-hospital mortality: Summary scores as a categorical variable, For 1-year mortality: Summary scores as a continuous variable	Logistic regression	<u>In-hospital mortality:</u> No results from unadjusted models. Results from adjusted models: 1 vs 0: OR=1.36 (95%CI: 1.16-1.60) 2 vs 0: OR=1.65 (95%CI: 1.38-1.97) ≥3 vs 0: OR=2.20 (95%CI: 1.86-2.57) <u>1-year mortality:</u> No results from unadjusted models. Results from adjusted models: OR=1.44 (95%CI: 1.36-1.53)
Zhang 2020[a]	In-hospital mortality, MACCE, Major bleeding, Acute ischemic stroke	CCI/Deyo (17 comorbidities)	CCI as prognostic factor; Summary scores as a categorical variable (0, 1, 2, ≥3); In sensitivity analysis, summary scores as a continuous variable.	Logistic regression	No results from unadjusted models. <u>In-hospital mortality:</u> Results from adjusted models: 1 vs 0: OR=1.31 (95%CI: 1.29-1.34) 2 vs 0: OR=1.45 (95%CI: 1.41-1.50) ≥3 vs 0: OR=1.74 (95%CI: 1.68-1.79) OR=1.13 (95%CI: 1.12-1.14) <u>In-hospital MACCE:</u> Results from adjusted models: 1 vs 0: OR=1.23 (95%CI: 1.20-1.25) 2 vs 0: OR=1.35 (95%CI: 1.32-1.38) ≥3 vs 0: OR=1.70 (95%CI: 1.66-1.75) OR=1.13 (95%CI: 1.12-1.14) <u>In-hospital Major bleeding:</u> Results from adjusted models: 1 vs 0: OR=1.16 (95%CI: 1.13-1.18) 2 vs 0: OR=1.33 (95%CI: 1.29-1.37) ≥3 vs 0: OR=1.64 (95%CI: 1.59-1.69) OR=1.12 (95%CI: 1.12-1.13) <u>In-hospital Acute ischemic stroke:</u> Results from adjusted models: 1 vs 0: OR=1.26 (95%CI: 1.21-1.31)

Study ID	Outcomes	Comorbidity measure used	prognostic factor/covariate; type of variable	Modelling	Final prognostic effect estimates for comorbidity measure (unadjusted and adjusted by other covariates)
					2 vs 0: OR=1.48 (95%CI: 1.41-1.55) ≥3 vs 0: OR=2.35 (95%CI: 2.23-2.46) OR=1.18 (95%CI: 1.17-1.19) OR of Individual comorbidities for each outcome in Supplementary Table 4 in the paper.
Zhang 2020[b]	In-hospital mortality, MACCE, Major bleeding, Acute ischemic stroke	ECS (30 conditions)	ECS as prognostic factor; Summary scores as a categorical variable (<0, 0, 1-5, 6-13, ≥14); Summary number of comorbidity conditions as a categorical variable (0, 1, 2, 3, 4, ≥5); In sensitivity analysis, summary scores and number of comorbidity conditions as a continuous variable;	Logistic regression	No results from unadjusted models. <u>In-hospital mortality:</u> Results from adjusted models: 0 vs <0: OR=1.25 (95%CI: 1.20-1.30) 1-5 vs <0: OR=2.16 (95%CI: 2.09-2.24) 6-13 vs <0: OR=3.30 (95%CI: 3.18-3.41) ≥14 vs <0: OR=4.81 (95%CI: 4.60-5.02) 1 vs 0: OR=0.95 (95%CI: 0.92-0.98) 2 vs 0: OR=1.06 (95%CI: 1.02-1.09) 3 vs 0: OR=1.19 (95%CI: 1.14-1.24) 4 vs 0: OR=1.36 (95%CI: 1.30-1.41) ≥5 vs 0: OR=1.65 (95%CI: 1.58-1.72) ECS: OR=1.08 (95%CI: 1.07-1.09) NEC: OR=1.11 (95%CI: 1.10-1.12) <u>In-hospital MACCE:</u> Results from adjusted models: 0 vs <0: OR=1.11 (95%CI: 1.08-1.14) 1-5 vs <0: OR=1.79 (95%CI: 1.75-1.84) 6-13 vs <0: OR=2.86 (95%CI: 2.78-2.94) ≥14 vs <0: OR=4.65 (95%CI: 4.49-4.82) 1 vs 0: OR=0.98 (95%CI: 0.95-1.00) 2 vs 0: OR=1.08 (95%CI: 1.04-1.11) 3 vs 0: OR=1.22 (95%CI: 1.18-1.26) 4 vs 0: OR=1.37 (95%CI: 1.32-1.43) ≥5 vs 0: OR=1.69 (95%CI: 1.63-1.76)

Study ID	Outcomes	Comorbidity measure used	prognostic factor/covariate; type of variable	Modelling	Final prognostic effect estimates for comorbidity measure (unadjusted and adjusted by other covariates)
					ECS: OR=1.08 (95%CI: 1.07-1.09) NEC: OR=1.12 (95%CI: 1.11-1.13) <u>In-hospital Major bleeding:</u> Results from adjusted models: 0 vs <0: OR=0.61 (95%CI: 0.59-0.63) 1-5 vs <0: OR=1.10 (95%CI: 1.07-1.14) 6-13 vs <0: OR=1.49 (95%CI: 1.45-1.54) ≥14 vs <0: OR=2.34 (95%CI: 2.25-2.45) 1 vs 0: OR=1.12 (95%CI: 1.07-1.16) 2 vs 0: OR=1.31 (95%CI: 1.26-1.36) 3 vs 0: OR=1.58 (95%CI: 1.51-1.66) 4 vs 0: OR=1.93 (95%CI: 1.84-2.04) ≥5 vs 0: OR=2.59 (95%CI: 2.46-2.72) ECS: OR=1.06 (95%CI: 1.05-1.07) NEC: OR=1.19 (95%CI: 1.18-1.20) <u>In-hospital Acute ischemic stroke:</u> Results from adjusted models: 0 vs <0: OR=0.98 (95%CI: 0.92-1.03) 1-5 vs <0: OR=1.50 (95%CI: 1.41-1.58) 6-13 vs <0: OR=3.03 (95%CI: 2.85-3.21) ≥14 vs <0: OR=6.00 (95%CI: 5.61-6.42) 1 vs 0: OR=1.28 (95%CI: 1.18-1.38) 2 vs 0: OR=1.64 (95%CI: 1.52-1.77) 3 vs 0: OR=2.00 (95%CI: 1.84-2.16) 4 vs 0: OR=2.31 (95%CI: 2.13-2.51) ≥5 vs 0: OR=2.98 (95%CI: 2.73-3.24) ECS: OR=1.10 (95%CI: 1.09-1.11) NEC: OR=1.19 (95%CI: 1.18-1.20)

Study ID	Outcomes	Comorbidity measure used	prognostic factor/covariate; type of variable	Modelling	Final prognostic effect estimates for comorbidity measure (unadjusted and adjusted by other covariates)
					OR of Individual comorbidities for each outcome in Supplementary Table 5 in the paper.
Pastor 2019	6-month all-cause mortality, 6-month readmissions (NA)	CCI (unknown version)	CCI as prognostic factor; Summary scores as a continuous variable; Summary scores quartile to 4 categories (cut-off values varied, no further information found).	Cox proportional hazard regression	No results from unadjusted models. <u>6-month mortality (not complete):</u> Results from adjusted models: HR=1.15 (95%CI: 1.06-1.26) 4 vs 1: HR=6.19 (95%CI: 2.95-12.95) <u>6-month readmissions(not complete):</u> Results from adjusted models: HR=1.15 (95%CI: 1.06-1.26) 4 vs 1: HR= NA

Study ID	Outcomes	Comorbidity measure used	prognostic factor/covariate; type of variable	Modelling	Final prognostic effect estimates for comorbidity measure (unadjusted and adjusted by other covariates)
Hautamäki 2020	1-month all-cause mortality, 6-month all-cause mortality, 2-year all-cause mortality,	The original CCI (19 conditions)	CCI as prognostic factor; Summary scores as a continuous variable; Individual comorbidity conditions	Cox proportional hazard regression	1-month mortality: Results from unadjusted models: HR=1.40 (95%CI: 1.31-1.51) Results from adjusted models: HR=1.14 (95%CI: 1.03-1.25) 6-month mortality: Results from unadjusted models: HR=1.43 (95%CI: 1.34-1.52) Results from adjusted models: HR=1.19 (95%CI: 1.10-1.29) 2-year mortality: Results from unadjusted models: HR=1.45 (95%CI: 1.38-1.52) Results from adjusted models: HR=1.25 (95%CI: 1.18-1.33) HR of Individual comorbidities for each outcome in Table 2 and 3 in the paper.

CCI: Charlson comorbidity index; HR: hazard ratio; CI: confidence interval; SAMI: Soroka acute myocardial infarction; OR: odd ratio; SCM: simplified comorbidity measure; SCI: simple comorbidity index; CS: chronic comorbidity score; HF: heat failure; MACE: major acute cardiovascular events; NA: not available; ECS: Elixhauser comorbidity score; MACCE: major acute cardiovascular and cerebrovascular events.

APPENDIX III: THESIS RELATED PUBLICATIONS

Appendix 1: Impact of Charlson Co-Morbidity Index Score on Management and Outcomes After Acute Coronary Syndrome.

Impact of Charlson Co-Morbidity Index Score on Management and Outcomes After Acute Coronary Syndrome

Fangyuan Zhang, MSc[a,*], Aditya Bharadwaj, MD[b,*], Mohamed O. Mohamed, MRCP(UK)[a,c,*], Joie Ensor, PhD[d], George Peat, PhD[d], and Mamas A. Mamas, DPhil[a,c,d,**]

Patients presenting with acute coronary syndrome (ACS) are frequently co-morbid. However, there is limited data on how co-morbidity burden impacts their receipt of invasive management and subsequent outcomes. We analyzed all patients with a discharge diagnosis of ACS from the National Inpatient Sample (2004 to 2014), stratified by Charlson Co-morbidity Index (CCI) into 4 classes (CCI 0, 1, 2, and ≥3). Regression analyses were performed to examine associations between co-morbidity burden and receipt of invasive intervention and in-hospital clinical outcomes. Of all 6,613,623 ACS patients analyzed, the prevalence of patients with severe co-morbidity (CCI ≥3) increased from 10.8% (2004) to 18.1% (2014). CCI class negatively correlated with receipt of invasive management, with CCI ≥3 group being the least likely to receive coronary angiography and percutaneous coronary intervention (odds ratio (OR) 0.42 95% confidence interval [CI] 0.41 to 0.43 and OR 0.47, 95% CI 0.46 to 0.48, respectively). CCI class was independently associated with an increased risk of mortality and complications, especially CCI ≥3 that was associated with significantly increased odds of Major Acute Cardiovascular & Cerebrovascular Events (OR 1.70, 95% CI 1.66 to 1.75), mortality (OR 1.74, 95% CI 1.68 to 1.79), acute ischemic stroke (OR 2.35, 95% CI 2.23 to 2.46), and major bleeding (OR 1.64, 95% CI 1.59 to 1.69). Co-morbidity burden has significantly increased amongst those presenting with ACS over an 11-year period and correlates with reduced likelihood of receipt of invasive management and increased odds of mortality and adverse outcomes. In conclusion, objective assessment of co-morbidities using CCI score identifies high-risk ACS patients in whom targeted risk reduction strategies may reduce their inherent risk of mortality and complications. **(Am J Cardiol 2020;130:15–23)**

Cardiovascular disease remains the leading cause of death in the United States (US).[1] A significant proportion of patients with CAD have concurrent co-morbid conditions.[2,3] Although at an individual level, a patient's co-morbidities affects treatment strategy, rehabilitation potential, and prognosis; at a population level co-morbid burden has a bearing on the utilization of healthcare resources.[4] Co-morbidities rarely occur in isolation and should be considered in totality, considering both cardiovascular and noncardiovascular conditions.[5,6] The Charlson Co-morbidity Index (CCI) is a measure of co-morbidity burden and provides a means of quantifying the prognostic impact of 22 co-morbid conditions on the basis of their number and individual impact by means of a score that was developed as a prognostic indicator for patients with a variety of medical conditions and has been shown to predict mortality, morbidity, risk of repeat hospitalizations, length of stay and cost of treatment.[3,7,8] Previous studies evaluating the impact of CCI on outcomes in acute coronary syndrome (ACS) have generally been limited to single-center studies,[9] small sample sizes,[10] specific cohorts of patients, such as first time hospitalization for acute myocardial infarction),[11] ST-segment elevation myocardial infarction (STEMI),[12] or focused only on incidence of ACS and not outcomes.[13] Furthermore, there is limited data on temporal trends and incidence of cardiovascular and noncardiovascular co-morbidities from a national perspective and their influence on the management and outcomes of ACS patients. As such, the present study examined temporal trends in co-morbidity burden, as measured by CCI score, amongst patients with ACS, and evaluated its impact on utilization of invasive management and subsequent clinical outcomes in a nationwide cohort of US hospitalizations.

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See page 22 for disclosure information.

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Methods

The data are extracted from the National Inpatient Sample (NIS)—the largest publicly available all-payer inpatient healthcare database in the United States. Further information on NIS dataset is available in Supplementary Appendix A.

The study period was from January 2004 to December 2014. All adults (≥18 years) with the principal diagnosis of ACS were eligible for inclusion and identified by

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Appendix 2: Temporal Trends in Comorbidity Burden and Impact on Prognosis in Patients With Acute Coronary Syndrome Using the Elixhauser Comorbidity Index Score.

Temporal Trends in Comorbidity Burden and Impact on Prognosis in Patients With Acute Coronary Syndrome Using the Elixhauser Comorbidity Index Score

Fangyuan Zhang, MSc[a,#], Mohamed O. Mohamed, MRCP(UK)[a,b,#], Joie Ensor, PhD[c], George Peat, PhD[c], and Mamas A. Mamas, DPhil[a,b,*]

Despite current evidence, little is known about the impact of comorbidity burden on invasive management strategies and clinical outcomes in the context of acute coronary syndrome (ACS). All ACS hospitalizations between 2004 and 2014 from the National Inpatient Sample were included, stratified by Elixhauser Comorbidity Score (ECS) and number of Elixhauser Comorbidities (NEC) to compare the receipt of invasive management and clinical outcomes between different ECS and NEC classes to the lowest class of either measure. A total of 6,613,623 records with ACS were included in the analysis. Overall comorbidity burden increased over the 11-year period, with higher comorbidity classes (ECS ≥ 14 and NEC ≥ 5) increasing from 2.1% to 4.6% and 4% to 16%, respectively. Higher ECS and NEC classes negatively correlated with the rates of utilization of coronary angiography (CA) and percutaneous coronary intervention (PCI) (ECS ≥14 vs <0: CA: 38.2% vs 69.3%, PCI: 18.6% vs 45.3%; NEC ≥5 vs 0: CA: 49.3% vs 73.4%, PCI: 24.4% vs 57.4%). Overall, higher ECS and NEC classes were independently associated with significantly increased odds of all complications, including major acute cardiovascular and cerebrovascular events, mortality, stroke and bleeding. In conclusion, among patients hospitalized for ACS, a higher comorbidity number or severity is associated with lower rates of receipt of CA and PCI, but not coronary artery bypass grafting, and worse clinical outcomes. Comorbidity burden assessment using ECS can help stratify patient groups at greatest risk of adverse outcomes in which invasive management is currently underutilized. **(Am J Cardiol 2020;125:1603–1611)**

Increased life expectancy and advancements in medical care have led to a rise in the number of patients living with comorbidities, who represent a significant proportion of those presenting with acute coronary syndrome (ACS).[1] Comorbidities rarely occur in isolation and many patients presenting with ACS have several comorbidities. However, only a few studies examined the association between comorbidity and ACS outcomes, and their findings were limited by single center analyses, small sample size and the analysis of specific cohorts (e.g., first time myocardial infarction [MI]), geographical regions or outcomes (e.g., mortality).[2–7] Therefore, the current evidence does not inform physicians of the patterns of comorbidity burden in this high-risk group, and whether this burden has changed over time in line with the shift in patient sociodemographics. Furthermore, it is unclear whether there is a difference in the management strategy offered to patients based on comorbidity burden, and whether the latter has an impact on clinical outcomes. The modified Elixhauser Comorbidity Score (ECS) is a well validated measure of comorbidity using administrative datasets that has been shown to be superior to Charlson Comorbidity Index (CCI) in cardiovascular and surgical cohorts.[2,8–10] The present study was designed to examine national estimates of the prevalence and temporal trends of comorbidity burden in patients presenting with ACS in the US, and the associations between comorbidity burden and in-hospital management strategy and clinical outcomes.

Methods

The National Inpatient Sample (NIS) is the largest publicly available all-payer of hospitalized patients in the United States and is sponsored by the Agency for Health Research and Quality as a part of the Healthcare Cost and Utilization Project.[11] NIS includes anonymized data on discharge diagnoses and procedures from more than 7 million hospitalizations annually. The NIS dataset constitutes a 20% stratified sample of US community hospitals and provides sampling weights to calculate national estimates that represent more than 95% of the US population. The NIS database has 15 diagnoses codes and 15 procedures codes for each hospital discharges record from the year 2004 to 2008. The number of diagnoses codes have been extended to 25 from the year

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Appendix 3: Prognostic impact of comorbidity measures on outcomes following acute coronary syndrome: A systematic review.

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SYSTEMATIC REVIEW
Cardiovascular medicine

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Prognostic impact of comorbidity measures on outcomes following acute coronary syndrome: A systematic review

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Abstract

Aim: To identify existing comorbidity measures and summarise their association with acute coronary syndrome (ACS) outcomes.

Methods: We searched published studies from MEDLINE (OVIDSP) and EMBASE from inception to March 2021, studies of the pre-specified conference proceedings from Web of Science since May 2017, and studies included in any relevant systematic reviews. Studies that reported no comorbidity measures, no association of comorbid burden with ACS outcomes, or only used a comorbidity measure as a confounder without further information were excluded. After independent screening by three reviewers, data extraction and risk of bias assessment of each included study was undertaken. Results were narratively synthesised.

Results: Of 4166 potentially eligible studies identified, 12 (combined n = 6 885 982 participants) were included. Most studies had a high risk of bias at quality assessment. Six different types of comorbidity measures were identified with the Charlson comorbidity index (CCI) the most widely used measure among studies. Overall, the greater the comorbid burden or the higher comorbidity scores recorded, the greater was the association with the risk of mortality.

Conclusion: The review summarised different comorbidity measures and reported that higher comorbidity scores were associated with worse ACS outcomes. The CCI is the most widely measure of comorbid burden and shows additive value to clinical risk scores in use.

Review criteria

Observational studies reporting associations between comorbidity measures and ACS outcomes were identified using bibliographical searches of Medline, EMBASE and Web of Science. All articles were screened for eligibility using the pre-defined inclusion criteria. Meta-analysis was not possible due to differences in the study designs and outcomes in different studies.

Message for the clinic

CCI is the most widely used comorbidity measure to investigate the relationship between comorbid burden and outcomes in patients with ACS. While comorbidity burden according to all

Appendix 4: Elixhauser outperformed Charlson comorbidity index in prognostic value after ACS: insights from a national registry.

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Journal of Clinical Epidemiology

ORIGINAL ARTICLE

Elixhauser outperformed Charlson comorbidity index in prognostic value after ACS: insights from a national registry

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Abstract

Objective: To compare the performance of risk adjustment models using the Elixhauser and Charlson comorbidity scores in predicting in-hospital outcomes of ACS patients from a nationwide administrative database.

Study Design and Setting: All hospitalizations for ACS in the United States between 2004 and 2014 (n = 7,201,900) were retrospectively analyzed. We used ECS and CCI score based on ICD-9 codes to define comorbidity variables. Logistic regression models were fitted to three in-hospital outcomes, including mortality, Major Acute Cardiovascular & Cerebrovascular Events (MACCE) and bleeding. The prognostic values of ECS and CCI after adjusting for known confounders, were compared using the C-statistic, Akaike information criterion (AIC), and Bayesian information criterion (BIC).

Results: The statistical performance of models predicting all in-hospital outcomes demonstrated that the ECS had superior prognostic value compared to the CCI, with higher C-statistics and lower AIC and BIC values associated with the former.

Conclusion: This is the first study that compared the prognostic value of the ECS and CCI scores in predicting multiple ACS outcomes, based on their scoring systems. Better discrimination and goodness of fit was achieved with the Elixhauser method across all in-hospital outcomes studied.

Keywords: Acute coronary syndrome; Comorbidity index; Charlson score; Elixhauser score; Model performance; Model comparison

What is new?

- This is the first study to comprehensively compare the performance of the ECS and CCI comorbidity scores in predicting ACS outcomes. The outcomes include mortality, major acute cardiovascular & cerebrovascular events (MACCE) and major bleeding.
- The findings indicate ECS has a higher prognostic value than CCI in terms of the statistical performance of models predicting all in-hospital outcomes.
- The findings imply that clinical practitioners should routinely adopt ECS to inform the risk stratification and management of ACS.

1. Introduction

Acute coronary syndrome (ACS) accounts for approximately 13% of deaths a year in the United States [1] and is commonly encountered in elderly populations who are increasingly multimorbid, due to increases in life expectancy and advances in medical care [2–4]. Comorbidity is defined as the coexistence of multiple conditions that coexist with an index medical condition at an individual patient level [5]. ACS rarely occurs in isolation, with patients often having more than one additional co-morbid condition [6–8]. The burden of comorbidity is important in patients

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