Developing predictive models for postoperative complications in cardiac patients

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This thesis is the result of the author's original research. It has been composed by the author and has not been previously submitted for examination which has led to the award of a degree.

Signed:

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Abstract

A number of cardiac preoperative risk stratification tools have been developed to predict mortality, and less often mortality and morbidity in surgery. Depending on their severity, postoperative complications can have a significant impact on patients' quality of life, hospital length of stay, and healthcare costs and resource usage. Nevertheless, mortality often remains the main 'key performance indicator' used in surgery and is the most commonly reported outcome when evaluating cardiac risk scores.

In this thesis, cardiac data in Golden Jubilee National Hospital was analysed to develop predictive models for postoperative complications in patients undergoing coronary artery bypass graft (CABG), valve, and combined valve and CABG surgery.

All patients undergoing cardiac surgery, recorded in the Golden Jubilee National Hospital CaTHI database between 1st April, 2012 and 31st March, 2016, were analysed.

Three outcomes were investigated: (a) if the patient had postoperative complications, (b) if the patient had severe postoperative complications, and (c) the level of postoperative complications. For each outcome, prediction models were developed, using logistic regression (a, b) and ordinal logistic regression (c). The performance of the models was measured, using receiver operating characteristic (ROC) curves (a, b) and confusion matrices (c), and compared with the performance of the logistic EuroSCORE predicting each outcome.

Of 3700 admissions, 59.7% had CABG, 26.4% valve, and 13.9% combined CABG and valve surgery. Overall, 48.65% of the patients had postoperative complications, with the prevalence of mild complications being 7.05%, moderate 36.65%, and severe complications being 4.95%.

For the model (a) predicting postoperative complications, the area under the ROC curve (AUC) was 0.636 with the sensitivity of 65.7% and specificity of 54.6%. For the model (b) predicting severe postoperative complications, the AUC of the local model was 0.685, with the sensitivity of 86.9% and specificity of 46.8%. The model (c) predicting the level of postoperative complications resulted with the confusion

matrix, where the accuracy for predicting no complications was 58%, mild 92%, moderate 63% and severe complications 95%.

Being the most accurate based on AUC, the local model predicting severe complications included eight variables: age, sex, diabetes, left ventricular function, previous cardiac surgery, hypertension, active endocarditis and previous myocardial infarction.

The variables associated with severe complications and the local model predicting severe complications could help the clinicians identify which patients are more likely to have severe complications in order to allocate resources accordingly.

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Chapter One: Introduction

1.1. Preoperative assessment

Preoperative services in NHS Scotland have been developed in the past decade to reduce cancellations of surgeries and to increase the ratio of day-case surgery. The preoperative assessment is a crucial step to detect potential problems early in order to manage the pathway for surgery effectively. (Bouamrane & Mair, 2014)

Preoperative assessment aims to assess patients' overall health status, identify unknown conditions that could lead to problems during and after surgery, to assess perioperative risk and to develop an appropriate perioperative care plan (Zambouri, 2007).

Previous studies have shown that preoperative clinics contribute to reducing hospital length of stay (Halaszynski, et al., 2004), cancellations and delays of operations (Ferschl, et al., 2005), preoperative costs (Foss & Apfelbaum, 2001), as well as improving patient safety and satisfaction (Hepner, et al., 2004). However, personal clinical judgement is not a reliable way to predict adverse outcome (Liao & Mark, 2003). Therefore, a variety of risk assessment tools have been developed to help clinicians calculate perioperative risks of mortality and less often morbidity, objectively.

1.2. Measuring risk

One of the earliest risk stratification tools was developed in 1928: to provide a common language for physicians, the New York Heart Association (NYHA) classification was published to provide a straight-forward way of classifying the severity of heart failure based on defined categories (e.g. shortness of breath, limited movement) (The Criteria Committee of the NYHA, 1994). Later, the American Society of Anaesthesiologists classification, approved in 1941, was the first systematic attempt to stratify risk for patients undergoing anaesthesia, based on specific needs and risks of the patient (Saklad, 1941).

Currently, various risk scores have been developed for numerous purposes, most scoring systems and models having been designed to predict mortality. Although, postoperative morbidity is acknowledged as the major factor of increased healthcare cost and significantly worsened quality of life after surgery (Lok, et al., 2004; Hein, et al., 2006; Hobson, et al., 2009), mortality is often the sole performance indicator used in surgery and is the most commonly reported outcome when it comes to evaluating risk scores (Poloniecki, et al., 1998).

Risk stratification tools in cardiac surgery are usually developed using multivariable analysis of risk factors for the observed outcomes (Adams & Leveson, 2012). The ideal risk prediction model is easy to calculate, reproducible, accurate, objective, cheap and possible to perform at the bedside (Barnett & Moonesinghe, 2011). Many risk scores require only a small number of routinely collected variables, and therefore are put into use in a clinical setting. However, with the aim of achieving greater predictive accuracy, some scores can include up to 30 variables, which makes collecting variables and calculation more complex. In addition, including many variables can result in a risk score being less reliable due to not all variables being available at a preoperative assessment centre. (Nashef, et al., 1999).

1.3. Aim of the study

In this thesis, data from cardiac audit database CaTHI and adult general intensive care unit (ICU) database WardWatcher, used in Golden Jubilee National Hospital, was analysed to develop predictive models for postoperative complications in patients undergoing cardiac surgery, specifically coronary artery bypass graft (CABG), valve, and combined valve and CABG surgery.

CABG is a type of surgery that improves blood flow to the heart, done for patients who have severe coronary heart disease (British Heart Foundation, 2017).

Coronary heart disease is a disease which causes a waxy substance called plaque building up inside the coronary arteries which supply oxygen-rich blood to the heart. As the plaque hardens, it can narrow the arteries, reducing the flow of oxygen-rich blood to the heart, which can cause chest pain or angina. During CABG, a healthy artery or vein from the body is connected to the blocked coronary artery, creating a new path for oxygen-rich blood to flow to the heart. (NHLBI, 2012)

The heart has four valves, which open and close in order to regulate the blood flow through different parts of the heart and ensuring that it travels in one direction. A patient is undergoing a valve surgery if the valve does not open fully and obstructs blood flow, or if the valve does not close properly, allowing blood to leak backwards. (British Heart Foundation, 2017)

The objectives of this thesis are (1) to identify risk factors associated with postoperative complications in Golden Jubilee National Hospital patient population undergoing coronary artery bypass graft (CABG), valve and combined CABG and valve surgery, (2) to develop a prediction model predicting postoperative complications in order to identify predictors for complications, and therefore (3) provide a starting point for establishing a prediction model in clinical practice.

In this thesis, the following questions are being answered:

- What are the risk factors of having postoperative complications for GJNH cardiac population?
- How do the locally developed prediction models perform when predicting (1) postoperative complications in general, (2) severe postoperative complications, and (3) the level of postoperative complications?
- How does logistic EuroSCORE perform when predicting (1) postoperative complications in general, (2) severe postoperative complications, and (3) the level of postoperative complications?
- How do the local models perform compared to logistic EuroSCORE?

In order to improve patients' quality of life after surgery and decrease healthcare costs, postoperative complications need to be investigated. Depending on the severity, postoperative complications can have a significant impact on patients' quality of life (Maillard, et al., 2015; Pinto, et al., 2016), increased hospital length of stay (Khan, et al., 2006; Yadla, et al., 2015; Abboud, et al., 2004; Diez, et al., 2007; Braxton, et al., 2004), and increased healthcare costs and resource usage (Zoucas, 2014; Eappen, et al., 2013; Wang & Chang, 2000; Ridderstolpe, et al., 2001; Salehi Omran, et al., 2007).

Postoperative complications are a major factor in delayed discharges, which is a problem for critical care (Majeed, et al., 2012). In June 2017 in NHS Scotland hospitals, 1,057 patients were delayed for more than three days, 27.6% of them being due to postoperative complications (ISD Scotland, 2017).

1.4. Structure of the Thesis

Chapter Two provides a background to the current problem of postoperative complications, including how the complications can affect patients' quality of life, hospital length of stay and healthcare costs.

Chapter Three provides a detailed review of the literature, where widely used preoperative cardiac risk stratification tools are tested at predicting postoperative complications. Each risk tool is introduced based on when they were developed and what they were initially designed to predict. The variables used to calculate scores are presented and explained why these would be connected to postoperative mortality and morbidity. Each investigated risk stratification tool is shown how they predict postoperative complications based on areas under the receiver operating characteristic curve in each study included in the literature review.

Chapter Four explains the methods used in the study, starting with ethics, data and participants, predictors used in order to predict models and outcomes for each model. Statistical analysis methods were explained, in particular, logistic regression, ordinal logistic regression, generalised linear model, generalised additive model, odds ratios, predicted probabilities, measuring model performance, and how each local model was compared with logistic EuroSCORE.

Chapter Five explains the study population with patient characteristics, and explains how cardiac, non-cardiac and other variables were distributed in the population of the study.

Chapter Six is about developing the model predicting postoperative complications. It starts with stating the variables associated with postoperative complications based on the population analysed, using unadjusted and adjusted odds ratios. Then the local model predicting postoperative complications is presented, showing the estimates of each variable included in the model, the receiver operating characteristic curve and predicted probabilities for patient having a postoperative complication. The association between logistic EuroSCORE and postoperative complications is shown, and the prediction model, where logistic EuroSCORE predicts postoperative complications is developed. The chapter ends with the comparison between the local model and logistic EuroSCORE based on the performance ability and variables used in the models.

Chapter Seven is about developing the model predicting severe postoperative complications, starting with the association between each variable and severe complication. The performance of the local model is explained based on receiver operating characteristic curves and predicted probabilities. Similarly to Chapter Five, logistic EuroSCORE model predicting severe postoperative complications is developed. The performance of both models is compared based on performance and variables used.

Chapter Eight firstly shows how variables are associated with the severity of postoperative complications. The local model predicting the level of postoperative complications is developed. Similar to previous models, also logistic EuroSCORE model predicting the level of postoperative complications is developed. The performance and variables of both models are compared.

Chapter Nine provides the discussion of the study, starting with the summary of all models developed, how they are compared to other prediction models in the literature in terms of performance and variables used. The results are discussed in terms of the research questions proposed in Chapter One, and the aims of the study. A discussion is provided to understand how this study can be useful for clinicians in preoperative assessment, and what could be learned in general from the results of the study.

Chapter Ten offers conclusions of the study, states some recommendations for future work in terms of postoperative complications, considers the contribution to knowledge and states the limitations of the study.

Chapter Two: The problem of postoperative complications

Coronary heart disease remains to be the leading cause of illness and death in Scotland, causing a higher rate of morality in Scotland (~100[1]), compared to United Kingdom as a whole (~80), and the European Union (~80) (ISD Scotland, 2016). In the UK, every year approximately 80% of deaths after a surgical procedure take place amongst high-risk of mortality patients who are estimated to make up approximately 10% of the overall inpatient surgical workload, and are a major source of not only mortality but also morbidity and resource usage (Findlay, et al., 2011; Hoogervorst-Schilp, et al., 2015).

In 2015, 68% of the patients in intensive care unit (ICU), and 65% of patients in high dependency unit (HDU) required advanced respiratory and organ support (Scottish Intensive Care Society, 2016).

Already acknowledged half a century ago by Williams, et al., common postoperative complications after cardiac surgery are arrhythmias, congestive heart failure, low cardiac output syndrome, renal complications, central nervous system complications, infections, pulmonary complications and hypertension (Williams, et al., 1965) - all of them are recognised as the reason for delayed discharges and the need for higher level of care (Al-Sarraf, et al., 2011; Knapik, et al., 2011; Bicer, et al., 2005; Hortal, et al., 2009; Ruel, et al., 2017).

Prolonged hospital and ICU length of stay, and ventilation

Prolonged ICU stay can adversely affect health by increased risk of infection, complications and mortality, and are known to consume a significant proportion of ICU resources resulting in increased healthcare costs (Aygencel & Turkoglu, 2011; Martin, et al., 2005). Usually the ICU stay is defined as prolonged if a patient stays in the ICU for longer than 2 days.

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[1] European age and sex standardised mortality rates per 100,000 population in 2010.

Prolonged mechanical ventilation and ICU stay after cardiac surgery is becoming more common due to patients undergoing heart surgery having poorer risk of mortality and morbidity profiles due to higher number of comorbidities than before (Trouillet, et al., 2009). It has been found that the highest risk factors for prolonged ventilation and ICU stay are emergency surgery, combined procedures, valve procedures, preoperative renal problems and stroke before surgery (Knapik, et al., 2011).

Renal complications

Renal failure is known to be one of the most prevalent major complications after cardiac surgery. (Bove, et al., 2009). The severity of renal complications is also highlighted by the fact that patients older than 65 with chronic kidney disease before surgery may need lifetime renal replacement therapy (Jose Olivero, et al., 2012).

Infections

Mediastinitis is known to be one of the severe complications in cardiac patients due to high in-hospital and also long-term mortality, increased length of hospital stay and increased healthcare costs (Abboud, et al., 2004; Diez, et al., 2007; Braxton, et al., 2004). According to a study, obesity and smoking are two risk factors for mediastinitis (Abboud, et al., 2004), but also chronic obstructive pulmonary disease (Diez, et al., 2007).

In the literature, deep sternal wound infection is known to be one of the most complex complications in cardiac surgery with a significant impact on postoperative mortality and healthcare costs (Wang & Chang, 2000; Ridderstolpe, et al., 2001; Salehi Omran, et al., 2007). Deep sternal wound infection has been widely researched, and risk factors include age, female sex, obesity, diabetes, smoking, recent use of antibiotics, chronic obstructive pulmonary disease, heart failure, kidney dysfunction and emergency surgery (Abboud, et al., 2004; Diez, et al., 2007; Robinson, et al., 2007; Gårdlund, 2007; Cayci, et al., 2008; Harrington, et al., 2004).

Sepsis occurs to be a rare event in cardiac patients, however is known to be a significant contributor to increased morbidity, mortality, hospital and ICU length of stay and healthcare costs (Slaughter, et al., 1993; Paternoster & Guarracino, 2016). There are several risk factors found for patient having sepsis after cardiac surgery. High level of endotoxin activity, which is associated with acute kidney injury and renal dysfunction are shown to be risk factors for sepsis (Klein, et al., 2011; Paternoster, et al., 2014). In addition, patients under ventilation for 48 hours, compared with 24 hours have increased risk of sepsis by 50% (Gelijns, et al., 2014). Diabetes is shown to be an important risk factor for sepsis amongst cardiac patients due to increasing levels of blood glucose and its variability (Michalopoulos, et al., 1998; Lols, et al., 2011; Furnary, et al., 2004).

Cardiac complications

Congestive cardiac failure is known to be the most common cause of death among CABG patients. Patients with previous cardiac surgery, emergency surgery, peripheral vascular disease, hypertension, diabetes, renal failure and severe infections have a higher risk of having congestive cardiac failure. (Surgenor, et al., 2001; Zile, et al., 2001; Boyer, et al., 2004)

Prolonged use of inotropes is largely connected to aging population undergoing cardiac surgery who are at increased risk for low cardiac output syndrome following surgery. Low cardiac output is one of the common complications that is associated with increased short- and long-term mortality and healthcare costs. (Maganti, et al., 2005; Maganti, et al., 2010) Although inotropes are effective in supporting cardiac output, the prolonged use can cause increased myocardial oxygen consumption, tachycardia and arrhythmias. (Gillies, et al., 2005)

Inotropes are agents that alter the force of muscular contractions and therefore affect the strength of contraction of heart muscle, and are used when there is low cardiac output (Berry & McKenzie, 2010).

Myocardial infarction (MI) is shown to be associated with significant increase of ICU length of stay, hospital stay and overall healthcare costs (Chen, et al., 2007).

Postoperative arrhythmia is a highly prevalent postoperative complication, which occurs in up to 40% of patients undergoing CABG surgery and 64% of patients undergoing valve surgery (Rho, 2009). Some risk factors found to be associated with re-intubation after CABG surgery are preoperative chronic obstructive pulmonary disease, preoperative chronic heart failure, postoperative relative hypoxemia, postoperative acute kidney injury and total mechanical ventilation time (Jian, et al., 2013).

Respiratory complications

The prevalence of pneumonia, also known as lung inflammation, can be up to 21% amongst cardiac patients after surgery (Topal, 2012). Pneumonia can be highly common amongst patients having prolonged ventilation after surgery (Hortal, et al., 2009; Bicer, et al., 2005; Morrow, et al., 2009). Many other risk factors for postoperative pneumonia have been identified: age (Bicer, et al., 2005; Hortal, et al., 2009), unnecessary use of antibiotics (Kinlin, et al., 2010; Soo Hoo, et al., 2005), emergency surgery (Bicer, et al., 2005; Kinlin, et al., 2010; Hortal, et al., 2009) and pre-operative renal dysfunction (Thakar, et al., 2003).

Acute respiratory distress syndrome is known to be a leading cause of postoperative respiratory failure amongst patients undergoing cardiac surgery, and is associated with high mortality (Weissman, 2004). The risk factors for acute respiratory distress syndrome are shown to be poor LVEF (Asimakopoulos, et al., 1999; Christenson, et al., 1996), high age (Chen, et al., 2016), post-operative low cardiac output (Christenson, et al., 1996), smoking (Christenson, et al., 1996; Kaul, et al., 1998), combined procedure (Christenson, et al., 1996; Kogan, et al., 2014) and emergency procedure (Christenson, et al., 1996; Kaul, et al., 1998).

Neurological complications

Stroke is known to be one of the complications after cardiac surgery that leads to increased rate of mortality, morbidity and increased healthcare costs (Hogue, et al., 1999). Known risk factors for postoperative stroke are history of neurological problems, diabetes, higher age and cerebrovascular disease (Gardner, et al., 1985; Reed, et al., 1988; Tuman, et al., 1992; Ricotta, et al., 1995; Shaw, et al., 1984).

Neurological complications after cardiac surgery are one of the most severe complications. Postoperative cognitive dysfunction has been shown to have major long-term consequences not only on mortality and hospital stay, but also on patient’s quality of life (Tan & Amoako, 2013; Newman, et al., 2001; Steinmetz, et al., 2009; Slater, et al., 2009).

Other complications

Patients undergoing re-operation can have an increased in-hospital mortality from 2.8% to 12%, indicating that re-operation is a significantly associated with higher mortality, but also increased likelihood of surgical site infection, renal insufficiency, and prolonged ICU stay (Ruel, et al., 2017). It is common for patients undergo re-operation due to bleeding after cardiac surgery (Kristensen, et al., 2012). The risk factors for re-operation due to bleeding are known to be increased age, low BMI and non-elective operation (Karthik, et al., 2004; Moulton, et al., 1996).

Intra-aortic balloon pump (IABP) is used to provide circulatory assistance and allow the heart to rest and recover after injury. Patients requiring IABP after surgery have high in-hospital mortality (Ramnarine, et al., 2005). It has been reported that the use of postoperative IABP has been increased due to aging population with more complex diseases (Christenson, et al., 2002; Hedenmark, et al., 1989).

Gastrointestinal complications are associated with high morbidity and mortality rates after cardiac surgery. Some of the most common gastrointestinal complications are intestinal ischemia (Mangi, et al., 2005), gastrointestinal bleeding (Jayaprakash, et al., 2004), acute cholecystitis (Passage, et al., 2007), acute pancreatitis (Poirier, et al., 2003) and ileus (Simic, et al., 1997).

Patients with multiple organ failure are reported to have poor quality of life for at least one year after discharge from the ICU (Nielsen, et al., 1997).

Summary

There are various postoperative complications following cardiac surgery that can have a significant effect on patients' quality of life, hospital length of stay, and healthcare costs. Some severe complications are shown to lead to early mortality. This highlights the importance of researching postoperative complications.

Chapter Three: Five commonly used preoperative cardiac risk stratification tools predicting postoperative complications: a literature review

There are numerous cardiac risk stratification tools developed to predict mortality or, both mortality and morbidity. Some are widely used in different cardiac centres around the world, some have been developed and validated for local use.

There are some well-known systematic reviews available investigating cardiac risk stratification tools, the two most cited being by Moonesinghe, et al. (Moonesinghe, et al., 2013), and by Barnett and Moonesinghe (Barnett & Moonesinghe, 2011). However, currently there is no systematic review available about cardiac risk scores predicting postoperative complications as a sole outcome of the study.

As emphasised in Chapter Two, postoperative complications can have a significant impact on patients' quality of life after surgery, prolonged hospital length of stay and increased healthcare costs. Despite some cardiac risk scores being developed for also predicting postoperative morbidity, mortality remains to be the main observed postoperative outcome in the literature.

In this review five existing cardiac risk scores are assessed at how they predict postoperative complications following coronary artery bypass graft (CABG), valve or combined CABG and valve surgery. Regardless of being initially developed to predict only mortality or both mortality and morbidity, the risk scores are compared based on how they predict individual and combined postoperative complications.

3.1. Methods

3.1.1. Data sources and search strategy

The search includes the articles published between the 1st January 1980 and 1st March 2017, and was undertaken using ProQuest, PubMed and additional hand search, using PubMed.

The ProQuest search was for “cardiac risk stratification tool” AND/OR “surgical risk stratification” AND/OR “surgical risk assessment” AND/OR “surgical risk prediction” AND/OR “surgical risk score” combined with “morbidity” OR “mortality and morbidity” AND/OR “complications”.

The PubMed search was done using EndNote search engine, where the search was also for “cardiac risk stratification tool” AND/OR “surgical risk stratification” AND/OR “surgical risk assessment” AND/OR “surgical risk prediction” AND/OR “surgical risk score” combined with “morbidity” OR “mortality and morbidity” AND/OR “complications”.

The risk stratification tools found in literature were all searched individually on PubMed with keywords “morbidity” AND/OR “postoperative complication”.

In addition to the above, the references were used from found papers in order to get more information about the risk scores.

3.1.2. Citation management

For the citation management and sorting the studies, EndNote was used. The Excel tables were created to state the characteristics of each study, including the name of first author, year of publication, country of study, patient population size, and type of surgery, risk scores involved in study, type of study, and outcomes stated in study. Based on the risk scores analysed in each study, the most commonly analysed risk scores were selected.

3.1.3. Eligibility criteria and analysis

The studies were eligible if:

- The study was in English
- The study was about risk scores used on adults

- Only coronary artery bypass graft (CABG), valve or combined CABG and valve surgeries were investigated in the study
- If the study investigated risk scores predicting morbidity or, mortality and morbidity

The studies were ineligible if:

- The study cohorts included patients who were not adults
- The study was in another language than English
- The study was not about surgical assessment
- If the surgery was other than CABG, valve or combined CABG and valve surgery
- If the study investigated risk scores predicting mortality only

The original development studies of the included scores were used for identifying variables used in scores.

The risk scores from eligible studies were analysed based on validation for predicting either specific postoperative complications or combined postoperative complications, and compared based on their performance in different institutions.

3.2. Study selection

As visualised in Figure 1, in the initial search, 710 articles on ProQuest and 576 articles on PubMed were listed. Firstly, the titles of the articles were screened to identify the articles, which were about comparing, validating or developing cardiac risk scores. The abstracts of the articles were reviewed in order to identify the risk score studied and if CABG or valve surgeries were investigated. Twenty-two extra papers were identified from the reference lists of the found articles and from hand search. Two papers were excluded due to not being in English. Eleven more papers were excluded due to the included risk scores not being analysed by any other studies. Six papers were excluded after reading the full text due to the scores being for operations with children. Twenty-nine papers were excluded due to analysing patients undergoing other cardiac procedures than CABG and/or valve surgery. Twenty-four papers were excluded due to having mortality as the only outcome of the study. Twenty-five papers were included in the final review: one review article, seven comparative studies, five development and validation studies, and twelve validation studies.

The characteristics and results of each study will be discussed in Section 3.5.

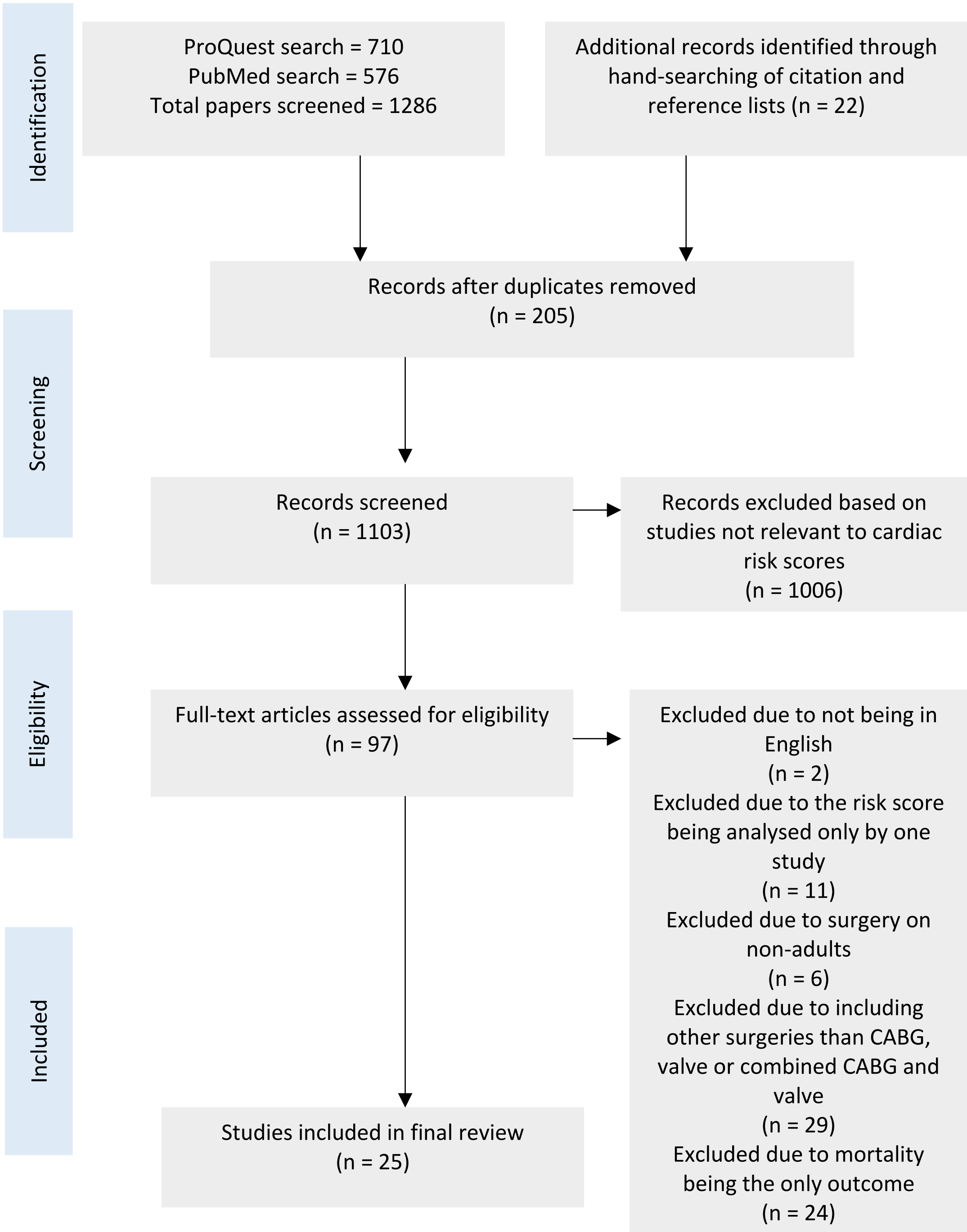

Figure 1: Flow diagram of study selection

3.3. Risk scores

Based on the papers included in the final review, three most cited cardiac risk assessment tools designed to predict postoperative mortality, and two cardiac risk assessment tools designed to predict postoperative mortality and morbidity were included in the literature review. These are Initial Parsonnet score, European System for Cardiac Operative Risk Evaluation (EuroSCORE) and EuroSCORE II designed to predict mortality, and Cleveland clinic, and The Society of Thoracic Surgeons (STS) score designed to predict mortality and morbidity. The information about the number of variables, author, development year, patient population, type of surgery and endpoints for each score in original studies can be found from Table 1.

Model	No. of variables	First author, year	No. of centres	Time-frame	N (Development)	N (Validation)	Type of surgery	Original Endpoint	Method of development
Initial Parsonnet Score	11	(Parsonnet, et al., 1989)	1 (Development), 3 (Validation)	1987-1988	3,500	1,332	Open-heart surgery	30-day mortality	Additive model
Cleveland Clinic Score	11	(Higgins, et al., 1992)	1	1986-1988 (Development); 1988-1990 (Validation)	5,051	4,069	CABG	In-hospital mortality, morbidity (MI, use of IABP, mechanical ventilation ≥ 3 days, neurological deficit, renal failure, serious infection)	Logistic regression
EuroSCORE	15	(Nashef, et al., 1999)	132	September – December 1995	13,302	1,479	Any cardiac surgery	In-hospital mortality	Logistic regression
STS Score	16	(Shroyer, et al., 2003)	589	1997-1999	403,325	100,153	CABG	30-day mortality, morbidity (stroke, renal failure, reoperation, prolonged ventilation, sternal infection)	Logistic regression
STS Score	16	(Shahian, et al., 2009)	819	2002-2006	464,929 for CABG, 65,855 valve procedures	309,952 for CABG, 43,904 for valve procedures	CABG and valve	In-hospital mortality, morbidity (renal failure, stroke, reoperation, prolonged ventilation, deep sternal wound infection, prolonged length of stay (>14 days), short length of stay (<6 days and alive))	Logistic regression
EuroSCORE II	17	(Nashef, et al., 2012)	154	3 May – 25 July 2010	16,828	5,553	Any cardiac surgery	In-hospital mortality	Logistic regression

Table 1: Characteristics of risk scores identified from the literature review

Initial Parsonnet Score

The Initial Parsonnet score, the oldest score of those reviewed, was developed by Victor Parsonnet, et al. in New Jersey as an additive scoring system to predict the 30-day mortality amongst 3,500 patients having an open-heart surgery. Including 11 variables, according to the Initial Parsonnet score, patients are categorised in five groups based on risk: good (0-4%), fair (5-9%), poor (10-14%), high (15-19%) and extremely high (20% or higher). Although Initial Parsonnet score was developed to predict 30-day mortality, the original study also states that the operative mortality had a high correlation with complication rates and hospital length of stay. (Parsonnet, et al., 1989)

Cleveland Clinic Score

The Cleveland Clinic score was developed in 1992 for stratifying risk of in-hospital mortality and postoperative morbidity in patients undergoing CABG surgery. The original study included 5051 Cleveland Clinic Foundation patients. The observed morbidities included myocardial infarction, use of intra-aortic balloon pump (IABP), mechanical ventilation for three or more days, neurological deficit, renal failure, or serious infection. Eleven variables were identified to be connected with mortality and postoperative morbidity. (Higgins, et al., 1992)

EuroSCORE

The European system for cardiac operative risk evaluation (EuroSCORE) was developed in 1999 in eight different European countries: Germany, France, UK, Italy, Spain, Finland, Sweden and Switzerland, including 132 centres. EuroSCORE was developed to predict in-hospital mortality amongst patients undergoing any cardiac surgery. Through analysis amongst 13,302 adult cardiac patients 15 variables were found that were associated with 30-day postoperative mortality. Initially an additive EuroSCORE was developed, with the risk groups being low (EuroSCORE 1-2), medium (EuroSCORE 3-5), and high (EuroSCORE 6 or higher). (Nashef, et al., 1999)

EuroSCORE was designed to be a user-friendly system for risk stratification, and therefore the initial study published only the additive version. Having been used widely in Europe and elsewhere, and with more developed information technology in more hospitals, logistic EuroSCORE was published for more accurate risk stratification. According to the authors, logistic EuroSCORE is more suitable for individual risk stratification in very high risk patients than additive EuroSCORE. (Roques, et al., 2003)

In addition, in order to make the calculation of EuroSCORE easier for clinicians, the developers have created an online calculator, which can be found from http://www.euroscore.org/calcold.html.

STS Score

The Society of Thoracic Surgeons (STS) risk adjustment models for adult cardiac surgery have been developed in different years in different stages, using the database that was started in 1992 in the United States, and now including more than 2 million cardiac procedures (Shahian, et al., 2009). The first STS model was developed in 2003 to predict 30-day mortality and morbidity after isolated CABG procedures. The predicted morbidities included length of stay, neurologic injury, prolonged ventilation, deep sternal wound infection, reoperation and renal failure. (Shroyer, et al., 2003) The most recent STS score, developed in 2009, predicts in-hospital mortality after isolated aortic valve replacement and morbidities such as sternal infection, reoperation, stroke, renal failure and prolonged ventilation (Shahian, et al., 2009).

STS score, including 16 variables, also has an online calculator available in order to make the calculation of the risk score easier for clinicians: http://riskcalc.sts.org/stswebriskcalc/#/calculate.

EuroSCORE II

EuroSCORE II was developed to update the existing EuroSCORE risk model to predict in-hospital mortality, including 22,381 patients undergoing any major cardiac surgery in 154 hospitals in 43 countries[2]. EuroSCORE II includes 17 variables found to be associated with postoperative mortality. Since improving the original

[2] Argentina (1 unit), Austria (2), Belarus (1), Belgium (8), Bosnia (1), Brazil (4), Canada (2), China (2), Croatia (2), Denmark (2), Finland (4), France (16), Germany (9), Greece (2), Holland (6), Hungary (1), India (4), Ireland (1), Israel (1), Italy (15), Japan (3), Lithuania (1), Montenegro (1), New Zealand (1), Norway (1), Poland (1), Portugal (4), Russia (3), Saudi Arabia (2), Serbia (4), Slovenia (1), South Africa (1), Spain (19), Sudan (1), Sweden (5), Switzerland (2), Syria (1), Taiwan (1), Turkey (1), UAE (1), UK (12), Uruguay (1), USA (3).

EuroSCORE model, several countries and institutions have validated EuroSCORE II. (Nashef, et al., 2012)

In order to make the calculation for EuroSCORE II easier for clinicians, the developers have created an online calculator, which can be found from http://www.euroscore.org/calc.html.

3.4. Variables used in the risk scores

All five risk scores, as seen in Table 2, include only pre-operative variables, meaning that all variables should be pre-operatively available. All scores include age, left ventricular (LV) function, pulmonary disease, previous cardiac surgery, type of surgery, and surgical priority variables. Sex, diabetes, neurological dysfunction and renal impairment are included in most scores.

Body mass index (BMI), previous myocardial infarction (MI) and angina status are needed to calculate three scores. Race, New York Heart Association (NYHA) classification and serum creatinine are used by only one score. The importance of some of these variables are largely backed up by the literature. However, some variables have less evidence why exactly they are used in the risk scores. The variables used less in the scores might be the reasons why risk scores perform differently in different patient populations.

	Designed to predict mortality			Designed to predict mortality and morbidity	
Variable	Logistic EuroSCORE	EuroSCORE II	Initial Parsonnet	STS	Cleveland Clinic
Reference	(EuroSCORE Study Group, 2011)	(EuroSCORE Study Group, 2011)	(Granton & Cheng, 2008)	(Granton & Cheng, 2008)	(Granton & Cheng, 2008)
Patient characteristics					
Age	x	x	x	x	x
BMI			x	x	x
Sex	x	x	x	x	
Race				x	
Diabetes		x	x	x	x
Cardiac variables					
LV function	x	x	x	x	x
Extracardiac arteriopathy	x	x			
Previous MI	x	x		x	
Preoperative IABP			x	x	
NYHA classification		x			
Angina status	x	x		x	
Active endocarditis	x	x			
Hypertension history	x	x			
Peripheral vascular disease				x	x
Non-cardiac variables					
Pulmonary disease	x	x	x	x	x
Neurological dysfunction	x	x		x	x
Renal impairment		x	x	x	x
Serum creatinine	x				
Surgical variables					
Previous cardiac surgery	x	x	x	x	x
Type of surgery	x	x	x	x	x
Critical preoperative state	x	x			
Surgical priority	x	x	x	x	x
TOTAL NUMBER OF VARIABLES	15	17	11	16	11

Table 2: The comparison between variables of cardiac risk assessment tools

3.4.1. Variables with agreed impact on postoperative outcome

There is a lot of information available in the literature why age, LV function, pulmonary disease, previous cardiac surgery, type of surgery, and surgical priority variables would be included in all scores.

Elderly patients have a higher risk of postoperative complications, especially for bleeding, infections, neurologic and pulmonary complications and renal problems (Wang, et al., 2014). In particular, elderly patients are shown to be more likely to have acute kidney injury (Jose Olivero, et al., 2012), deep sternal wound infection (Abboud, et al., 2004; Diez, et al., 2007; Robinson, et al., 2007; Gårdlund, 2007; Cayci, et al., 2008; Harrington, et al., 2004), pneumonia (Bicer, et al., 2005; Hortal, et al., 2009), stroke (Gardner, et al., 1985; Reed, et al., 1988; Tuman, et al., 1992; Ricotta, et al., 1995; Shaw, et al., 1984), acute respiratory distress syndrome (Chen, et al., 2016), bleeding (Karthik, et al., 2004; Moulton, et al., 1996), MI (Koniari, et al., 2011; Yau, et al., 2008), neurological complications (Arrowsmith, et al., 2000; Roach, et al., 1996; Baranowska, et al., 2012), and gastrointestinal complications (Andersson, et al., 2005).

LV function is shown to be associated with higher risk of mortality and complications after cardiac surgery (Pieri, et al., 2016), in particular associated with low cardiac output syndrome (Royster, et al., 1991), acute renal failure (Thakar, et al., 2003; Landoni, et al., 2007), respiratory failure, sternal wound infection, bleeding, stroke (Topkara, et al., 2005), low cardiac output (Ding, et al., 2015; de Oliveira Sá, et al., 2012) and adult respiratory distress syndrome (Asimakopoulos, et al., 1999; Christenson, et al., 1996).

Patients with pulmonary disease appear to have a higher rate of postoperative mortality (Adabag, et al., 2010; McKeon, et al., 2015), longer intubation time, and ICU and hospital stay than patients without pulmonary disease (McKeon, et al., 2015).

Patients with previous cardiac surgery have shown to have a higher risk of having congestive cardiac failure after surgery (Surgenor, et al., 2001; Boyer, et al., 2004; Zile, et al., 2001). It is explained by redo-surgery being technically challenging in terms of surgical approach (Jegaden, et al., 2012).

It is known that patients undergoing valve procedures or combined surgery have the highest mortality rate (Nicolini, et al., 2011). Patients undergoing aortic valve replacement and mitral valve replacement have significantly increased risk of short-term mortality compared to patients undergoing CABG surgery (Gardner, et al., 2004).

Patients undergoing emergency surgery are a challenge: important information, documentation and the results may not be accessible and the patient might not be able to contribute (Cornelissen & Arrowsmith, 2006). In addition, patients undergoing emergency cardiac surgery are known to have a higher risk of 30-day mortality than patients undergoing an elective CABG surgery (Khaladj, et al., 2013; Rastan, et al., 2006; Schumer, et al., 2016) and elective valve surgery (Lorusso, et al., 2008).

Diabetes, neurological and renal function, being included in most scores also have a generally agreed impact on postoperative outcome. EuroSCORE II and STS both include diabetes and renal impairment, the latter being interchangeable with serum creatinine variable, included in EuroSCORE.

Diabetes is shown to be a very large contributor when it comes to postoperative complications. Diabetics are shown to have higher risk of neurological (Arrowsmith, et al., 2000; Roach, et al., 1996; Baranowska, et al., 2012) and renal complications, prolonged ICU stay, bleeding (Morricone, et al., 1999) and wound infections (Järvinen, et al., 2005; Abboud, et al., 2004; Robinson, et al., 2007; Gårdlund, 2007; Cayci, et al., 2008; Harrington, et al., 2004). Diabetes is also shown to be a risk factor for postoperative congestive cardiac failure (Surgenor, et al., 2001; Boyer, et al., 2004; Zile, et al., 2001), stroke (Gardner, et al., 1985; Reed, et al., 1988; Tuman, et al., 1992; Ricotta, et al., 1995; Shaw, et al., 1984), low cardiac output (Tolpin, et al., 2009; Pan, et al., 2006) and sepsis (Michalopoulos, et al., 1998; Lols, et al., 2011; Furnary, et al., 2004).

Neurological dysfunction before cardiac surgery is associated with increased mortality and morbidity, including higher likelihood of having postoperative stroke and other central nervous complications following cardiac surgery (Arrowsmith, et al., 2000). Renal impairment is associated with low cardiac output, bleeding and prolonged ventilation after surgery (Al-Sarraf, et al., 2011), and extracardiac arteriopathy is shown to be a risk factor for decreased survival (Di Eusanio, et al., 2012; Järvinen, et al., 2005).

There are some variables that are not included in all scores, but can have an important impact on the outcome.

Various studies have shown that preoperative MI is associated with postoperative MI (Al-Attar, 2011; Livhits, et al., 2011; Koniari, et al., 2011; Yau, et al., 2008). In addition, patients with a previous MI are in a higher risk of having deep sternal wound infection (Abboud, et al., 2004; Diez, et al., 2007; Robinson, et al., 2007; Gårdlund, 2007; Cayci, et al., 2008; Harrington, et al., 2004).

Angina status is shown to be a significant predictor of long-term mortality (Kaul, et al., 2009), patients with high exercise performance having better survival than those with limited to low exercise capacity (Myers, et al., 2002; Dagenais, et al., 1982).

The variables similar between EuroSCORE and EuroSCORE II are extracardiac arteriopathy, active endocarditis, hypertension history and critical preoperative state.

Active endocarditis is shown to be associated with coronary heart failure (Hasbun, et al., 2003) and acute renal failure (Conlon, et al., 1998). Hypertension history is associated with stroke (Arrowsmith, et al., 2000; Roach, et al., 1996; Baranowska, et al., 2012), renal dysfunction, unstable angina, myocardial infarction and heart failure (Surgenor, et al., 2001; Zile, et al., 2001; Boyer, et al., 2004) (Varon & Marik, 2008).

Critical preoperative state is associated with prolonged mechanical ventilation and ICU stay (Knapik, et al., 2011), pneumonia (Thakar, et al., 2003), and prolonged use of inotropes (Gillies, et al., 2005). Having a critical preoperative state is shown to have an impact on early and late mortality after CABG surgery (Saxena, et al., 2011), but is also shown to be a risk factor for seizures after cardiac surgery (Goldstone, et al., 2011).

Although, the use of IABP and a peripheral vascular disease variable are only included in the STS score, they are both agreed to have an effect on the postoperative outcome. It has been found that the pre-operative use of IABP reduces mortality in elective high-risk CABG patients (Zangrillo, et al., 2015). The presence of peripheral vascular disease increases postoperative mortality amongst CABG patients (O'Connor, et al., 1992; Higgins, et al., 1992).

3.4.2. Variables with less evidence about impact on postoperative outcome

However, the importance of some variables is not so widely agreed on. In the literature, sex and previous cardiac surgery do create some differences in evidence.

It is often explained that sex is included in many risk scores due to the fact that women often lack chest pain (Canto, et al., 2007) which can delay diagnosis, and therefore could lead to more serious conditions such as shock, worsened ischemia and worsened MI (Sezai, et al., 2010). However, it has been found that although female patients in their patient cohort are often older and at higher risk, female gender is not an independent risk factor for postoperative mortality and morbidity (Trienekens, et al., 2015). It has also been suggested that that the lack of representation of women in older clinical trials has an effect of understanding of the management of coronary artery disease in women, and therefore further studies to evaluate gender-related differences in autonomic responses are needed (Koch & Nussmeier, 2003).

Also, the BMI, included in Initial Parsonnet, STS and Cleveland Clinic score, race, included only in STS score, and NYHA classification, included only in EuroSCORE II, are controversial.

It has been stated that obese patients have increased risk of wound infection, blood loss and longer operation time, however it is also said that having a higher BMI is associated with improved survival, compared to underweight patients (Tjeertes, et al., 2015; Reis, et al., 2008). Obesity can even have a protective effect when it comes to pulmonary dysfunction, re-admission and mortality, however is a risk factor for renal dysfunction (Reis, et al., 2008).

There is no particular reason found why race is included in STS score. Two studies suggest that excess mortality in ethnical minority groups undergoing cardiac surgery is due to their over-representation in low-quality hospitals, where all patients in spite of race have worse outcomes than patients in an average hospital (Khera, et al., 2015; Rangrass, et al., 2014).

When it comes to New York Heart Association grade, literature suggests there is no widespread agreement on how to assign a patient to a grade, which results in subjectivity and poor reproducibility (Raphael, et al., 2007).

As a conclusion, the variables included in EuroSCORE appear to be all considerably well backed up by the literature, whereas EuroSCORE II and STS score all include some factors that are either subjective or not very well explained.

3.5. The risk scores predicting postoperative complications

Based on the development studies, most scores were initially developed for risk stratification after CABG surgery. However, nowadays most scores are used for various cardiac procedures, including valve, CABG and combined valve and CABG surgeries.

Each score was described based on how they perform in different studies predicting morbidity, regardless of being initially designed for predicting mortality only, or both mortality and morbidity. The study characteristics can be found from Table 3, including all complications predicted in each study. In Sections 3.5.1 and 3.5.2 the performance at predicting individual and combined complications of each risk score is described.

The majority of the found studies are based in one hospital. Based on the number of patients involved in studies, a multi-centre study carried out in China by Wang, et al. (Wang, et al., 2014) stands out with involving 11,170 cardiac patients. Amongst single-centre studies, a study by Lawrence, et al. (Lawrence, et al., 2000) carried out in the UK analysing Initial Parsonnet Score has the largest patient population of 5591 patients. Fifteen studies analysed risk scores at predicting individual postoperative complications, nine studies analysed combined postoperative complications. There was a higher number of studies involving EuroSCORE than any other scores included in the review.

It should be noted, that not all complications are compared by all studies, and therefore the predictive ability of a risk score for complications across a few studies with different populations is not truly comparable. However the results do give an indication of the variability in the predictability of a particular complication across different studies.

Reference	Region	N	Multicentre	Risk scores included	Type of surgery	Type of study	Outcome	Complications predicted
(Biancari, et al., 2012)	Finland	1027	No	EuroSCORE II	CABG	Validation	Mortality and individual postoperative complications	**Individual:** ICU length of stay, dialysis, prolonged use of inotropes
(Borde, et al., 2013)	India	498	No	EuroSCORE II, STS	CABG, Valve, combined CABG and Valve	Validation	Mortality for EuroSCORE II and STS; individual postoperative complications for STS.	**Individual:** Length of stay, ventilation, renal failure, stroke, deep sternal wound infection, reoperation
(Candela-Toha, et al., 2008)	Spain	1867	No	Cleveland Clinic score	Any cardiac surgery	Validation	Individual postoperative complications.	**Individual:** Acute kidney injury
(Dupuis, et al., 2001)	Canada	3548	No	Parsonnet, CARE, Tuman	CABG, Valve, combined CABG and Valve	Comparative study	Mortality and combined postoperative complications	**Combined:** Length of stay, low cardiac output, hypotension, IABP use, ventilation, atrial fibrillation, tracheostomy, reintubation, neurologic problems, renal failure, sepsis, deep sternal wound infection
(Gabrielle, et al., 1997)	France	6649	Yes	Initial Parsonnet score	Any cardiac surgery	Validation	Combined postoperative complications.	**Combined:** Re-operation, low cardiac output, use of IABP, MI, ventricular arrhythmia, prolonged intubation, renal failure, severe infection, stroke, bleeding
(Geissler, et al., 2000)	German y	504	Yes	Initial Parsonnet score, Cleveland Clinic Score, French Score, EuroSCORE, Pons score, Ontario Province risk score	Any cardiac surgery with CABG	Comparative study	Mortality and combined postoperative complications.	**Combined:** Use of mechanical assist devices, renal failure, stroke, MI, prolonged ventilation, ICU stay
(Granton & Cheng, 2008)	Canada		N/A[3]	EuroSCORE, STS, Initial Parsonnet, Cleveland Clinic, NNE, SCTS	Any cardiac surgery	Review article	N/A	
(Hirose, et al., 2009)	Japan	1552	No	EuroSCORE	CABG	Validation	Mortality, individual postoperative complications, combined postoperative complications	**Individual:** Renal failure, congestive cardiac failure, pneumonia, stroke, mediastinitis, bleeding, MI, ICU stay, intubation time, length of stay; **Combined:** Congestive cardiac failure, mediastinitis, pneumonia, renal failure, stroke

[3] This is a literature review, where none of the risk scores were tested on a specific patient cohort.

Reference	Region	N	Multicentre	Risk scores included	Type of surgery	Type of study	Outcome	Complications predicted
(Lawrence, et al., 2000)	UK	5591	No	Initial Parsonnet score	Any cardiac surgery	Validation	Mortality and individual postoperative complications	**Individual:** Stroke, use of IABP, haemofiltration, tracheostomy, bleeding, ICU stay
(Messaoudi, et al., 2009)	Belgium	1562	No	EuroSCORE	CABG, Valve, combined CABG and Valve	Validation	Individual postoperative complications.	**Individual:** Prolonged ICU stay
(Nilsson, et al., 2004)	Sweden	3404	No	EuroSCORE	Open heart surgery	Validation	Individual postoperative complications.	**Individual:** ICU length of stay and ICU cost
(Pitkänen, et al., 2000)	Finland	4592	No	EuroSCORE and a locally derived model	Any cardiac surgery	Comparative study	Mortality, individual postoperative complications, combined postoperative complications	**Individual:** ICU length of stay; **Combined:** Anuria, bleeding, gastrointestinal complication, IABP use, mediastinitis, multi-organ failure, need for inotropes, neurological dysfunction, pneumonia, prolonged ventilation, re-admission to ICU, sepsis, stroke
(Scolletta, et al., 2004)	Italy	1090	No	Cleveland Clinic score	CABG	Validation	Combined postoperative complications.	**Combined:** Decreased oxygen delivery, need for inotropes
(Syed, et al., 2004)	Saudi Arabia	194	No	EuroSCORE, Parsonnet score	CABG	Comparative study	Mortality, individual postoperative complications, combined postoperative complications	**Individual:** Length of stay; **Combined:** Bleeding, deep wound infection, MI, renal impairment, stroke
(Toumpoulis, et al., 2005)	USA	5051	No	EuroSCORE	Any cardiac surgery	Validation	Mortality and individual postoperative complications	**Individual:** Renal failure, Sepsis
(Wang, et al., 2016)	New Zealand	450	No	EuroSCORE, EuroSCORE II, STS	Combined valve and CABG	Comparative study	Mortality, individual postoperative complications, combined postoperative complications	**Individual:** Deep sternal wound infection; **Combined:** Deep sternal wound infection, prolonged length of stay, prolonged ventilation, renal failure, return to theatre, stroke
(Wang, et al., 2017)	New Zealand	408	No	EuroSCORE, EuroSCORE II, STS	Mitral valve surgery	Comparative study	Mortality, individual postoperative complications, combined postoperative complications	**Individual:** Prolonged ventilation, renal failure, mediastinitis, prolonged length of stay; **Combined:** Mediatsinitis, prolonged hospital stay, prolonged ventilation, renal failure, return to theatre, stroke
(Wang, et al., 2014)	New Zealand	818	No	EuroSCORE, EuroSCORE II, STS, AusSCORE	CABG	Comparative study	Mortality and individual postoperative complications	**Individual:** Renal failure, deep sternal wound infection, stroke, congestive cardiac failure, pneumonia
(Wong, et al., 2015)	Canada	2316	No	Cleveland Clinic Score	Any cardiac surgery	Validation	Individual postoperative complications.	**Individual:** Acute kidney injury

Reference	Region	N	Multicentre	Risk scores included	Type of surgery	Type of study	Outcome	Complications predicted
(Wang, et al., 2014)	China	11170	Yes	EuroSCORE II	Valve surgery	Validation	Mortality, individual postoperative complications	**Individual:** ICU stay, prolonged ventilation, acute respiratory distress syndrome, renal failure

Table 3: Characteristics of studies included in the review, where S = single-centre, M = multi-centre

3.5.1. Preoperative risk scores predicting individual postoperative complications

From Table 4 we can see which scores have the best ability to predict certain complications. Most widely investigated complications include renal failure, prolonged ICU stay, ventilation time, hospital length of stay, mediastinitis and deep sternal wound infection. For these complications we have a better understanding about the risk score's performance amongst different populations.

Complication	Initial Parsonnet (No. of studies)	Cleveland Clinic (No. of studies)	STS (No. of studies)	EuroSCORE (No. of studies)	EuroSCORE II (No. of studies)
Prolonged ICU stay	0.70 (1)			0.76-0.78 (3)	0.66-0.79 (2)
Hospital length of stay	0.67 (1)		0.64 (1)		0.72 (1)
Renal failure		0.61-0.86 (2)	0.71-0.83 (3)	0.74-0.87 (3)	0.65-0.79 (2)
Prolonged ventilation			0.65-0.79 (2)	0.71-0.75 (2)	0.70-0.77 (2)
Mediastinitis			0.72 (1)	0.73-0.76 (2)	0.80 (1)
Deep sternal wound infection			0.63-0.89 (2)	0.57 (1)	0.65-0.72 (2)
Sepsis				0.74 (1)	
Congestive cardiac failure				0.86 (1)	
Pneumonia				0.81 (1)	
Stroke				0.74-0.77 (2)	
Postoperative dialysis					0.80 (1)
Prolonged use of inotropes					0.75 (1)
Acute respiratory distress syndrome					0.75 (1)

Table 4: The area under the receiver operating characteristic curve for each complication analysed in included studies

Prolonged hospital and ICU length of stay, and ventilation

EuroSCORE II is also shown to have the best performance at predicting hospital length of stay. For mitral valve surgery patients in New Zealand, EuroSCORE II has a moderate performance at predicting prolonged hospital length of stay (AUC=0.72) (Wang, et al., 2017). However, EuroSCORE II does not have a remarkably better performance, compared to the other scores. Initial Parsonnet score has also a moderate performance for hospital length of stay (AUC=0.67) in Saudi Arabian cardiac patients (Syed, et al., 2004), and so does STS score in CABG patients in India (AUC=0.64) (Borde, et al., 2013).

Based on the included studies, and compared to other scores, EuroSCORE has the best predictive ability for predicting prolonged ICU stay, in terms of consistent performance of the model. EuroSCORE is shown to predict ICU length of stay considerably well in Finnish (AUC=0.76) (Pitkänen, et al., 2000), Belgian (AUC=0.77) (Messaoudi, et al., 2009), and Swedish (AUC=0.78) (Nilsson, et al., 2006) single centre studies.

EuroSCORE II in Finland has also a very good performance (AUC=0.79) (Biancari, et al., 2012), however a moderate performance in a multicentre study in China (AUC=0.66) (Wang, et al., 2014). Prolonged ICU stay is also predicted moderately well by Initial Parsonnet score in a single centre in the UK (AUC=0.70) (Lawrence, et al., 2000).

The STS score has the best ability to predict prolonged ventilation. For patients undergoing mitral valve surgery in New Zealand, STS was shown to have a considerably good performance at predicting prolonged ventilation (AUC=0.79), slightly better than EuroSCORE II (AUC=0.77) and EuroSCORE (AUC=0.75) (Wang, et al., 2017). However, in India, STS seems to have a moderate performance (AUC=0.65) (Borde, et al., 2013).

For CABG patients, EuroSCORE has a moderate performance in New Zealand (AUC=0.71) (Wang, et al., 2014). For valve patients in China, EuroSCORE II has also a moderate performance when predicting ventilation hours (AUC=0.70) (Wang, et al., 2014).

Renal complications

Compared to other scores, EuroSCORE is also shown to have the best predictive ability for renal failure after surgery. EuroSCORE predicts renal failure considerably well in single centre studies in the US (AUC=0.80) (Toumpoulis, et al., 2005), Japan (AUC=0.87) (Hirose, et al., 2009) and New Zealand (AUC=0.74) (Wang, et al., 2017).

Renal failure is also predicted considerably well by Cleveland Clinic score in a single centre study in Spain (AUC=0.86) (Candela-Toha, et al., 2008), by STS score in India (AUC=0.79) (Borde, et al., 2013), in New Zealand for valve patients (AUC=0.83) (Wang, et al., 2017), and by EuroSCORE II in New Zealand (AUC=0.79) (Wang, et al., 2017). However, in CABG patients in New Zealand, STS score is shown to have a moderate performance at predicting renal failure (AUC=0.71) (Wang, et al., 2014).

A study analysing 2316 patients undergoing cardiac surgery who developed postoperative kidney injury, found that higher Cleveland Clinic score is associated with a higher risk of Stage 3 acute kidney injury, with the AUC for Stage 1 and Stage 2 being 0.61, and 0.78 for Stage 3 (Wong, et al., 2015). In CABG patients in Finland, EuroSCORE II is also shown to be predictive of dialysis (AUC=0.80) (Biancari, et al., 2012).

Infections

Compared to other scores, EuroSCORE II is the best at predicting mediastinitis. In a single centre study in New Zealand, EuroSCORE II predicts mediastinitis after mitral valve surgery considerably well (AUC=0.80). In the same study, EuroSCORE predicts mediastinitis moderately well (AUC=0.73), and so does STS (AUC=0.72). (Wang, et al., 2017) Mediastinitis is also predicted considerably well by EuroSCORE in Japan (AUC=0.76) (Hirose, et al., 2009).

Compared to other scores, STS score is also shown to have the best performance at predicting postoperative deep sternal wound infection. A single centre study in India found that for CABG patients, STS score predicts deep sternal wound infection very well (AUC=0.89) (Borde, et al., 2013).

In combined CABG and valve patients in New Zealand, EuroSCORE II has a moderate, although slightly better predictive ability for deep sternal wound infection (AUC=0.65) than EuroSCORE (AUC=0.57) and STS score (AUC=0.63) (Wang, et al., 2016). For CABG patients in New Zealand, EuroSCORE II has a moderate performance at predicting deep sternal wound infection (AUC=0.72) (Wang, et al., 2014).

In a single centre study in the US, EuroSCORE has a considerably good performance at predicting postoperative sepsis (AUC=0.74) (Toumpoulis, et al., 2005). Cardiac complications

EuroSCORE has a very good performance at predicting congestive cardiac failure (AUC=0.86) in a single-centre study in Japan (Hirose, et al., 2009). EuroSCORE II is shown to have a predictive ability for prolonged use of inotropes (AUC=0.75) in CABG patients in Finland (Biancari, et al., 2012).

Respiratory and neurological complications

A multicentre study in China investigating patients undergoing valve surgery found that EuroSCORE II shows a reasonable discrimination for postoperative complications such as acute respiratory distress syndrome (AUC=0.75) (Wang, et al., 2014). EuroSCORE is also shown to predict pneumonia (AUC=0.81) considerably well in a single-centre study in Japan (Hirose, et al., 2009)

Stroke is predicted by EuroSCORE relatively well (AUC=0.74) in CABG patients in New Zealand (Wang, et al., 2014), however has a slightly better performance in a single-centre study in Japan (AUC=0.77) (Hirose, et al., 2009).

3.5.2. Preoperative risk scores predicting combined postoperative complications

From Table 5 it can be seen how the risk scores perform at predicting combined postoperative complications that can have various risk factors. It can be also seen that different studies have different complications included in the combined outcome. There is no consistency in the approach taken for combining complications in the literature, and makes the comparison of the performance very difficult.

The commonly predicted combined complications include low cardiac output, the need for re-operation, using intra-aortic balloon pump (IABP), myocardial infarction, postoperative arrhythmia, the need for re-intubation, neurological complications, gastrointestinal complications and multiple organ failure. These complications can either have a major impact on patient’s quality of life, or increased healthcare costs.

A multicentre study in France found that the Initial Parsonnet score has a moderate predictive ability when predicting severe morbidity (AUC=0.64) after cardiac surgery in French patients (Gabrielle, et al., 1997), however, having a slightly better performance in Saudi Arabian patient cohort (AUC=0.66) (Syed, et al., 2004). Initial Parsonnet score performs the best in a Canadian single centre study where CABG, valve and combined CABG and valve procedures were investigated (AUC=0.73) (Dupuis, et al., 2001).

According to a single-centre study in the UK, patients with Initial Parsonnet score between 0 and 9 are less likely to have postoperative complications, such as stroke, the need for IABP, hemofiltration, bleeding and the need for tracheostomy (Lawrence, et al., 2000).

	Combined complications	AUC	Reference
Initial Parsonnet	Bleeding * IABP use * Low cardiac output * MI * Prolonged intubation * Re-operation * Renal failure * Severe infection * Stroke * Ventricular arrhythmia	0.64	(Gabrielle, et al., 1997)
	Acute renal failure * Atrial fibrillation * Brain injury * Deep sternal wound infection * Hypotension * IABP use * Leg wound * Low cardiac output * Prolonged ventilation * Reintubation * Septic shock * Tracheostomy	0.73	(Dupuis, et al., 2001)
	Bleeding * Deep wound infection * MI * Renal impairment * Stroke	0.66	(Syed, et al., 2004)
Cleveland Clinic	MI * Need for mechanical device * Prolonged ICU stay * Prolonged ventilation * Renal failure * Return to theatre * Stroke	0.69	(Geissler, et al., 2000)
STS	Mediastinitis * Prolonged hospital stay * Prolonged ventilation * Renal failure * Return to theatre * Stroke	0.73	(Wang, et al., 2017)
	Deep sternal wound infection * Prolonged hospital stay * Prolonged ventilation * Renal failure * Return to theatre * Stroke	0.63	(Wang, et al., 2016)
EuroSCORE	Anuria * Bleeding * Gastrointestinal complication * IABP use * Mediastinitis * Multi-organ failure * Need for inotropes * Neurological dysfunction * Pneumonia * Prolonged ventilation * Re-admission to ICU * Sepsis * Stroke	0.70	(Pitkänen, et al., 2000)
	Bleeding * ICU > 6days * MI * Need for mechanical device * Prolonged ventilation * Renal failure * Stroke	0.64	(Geissler, et al., 2000)
	Congestive cardiac failure * Mediastinitis * Pneumonia * Renal failure * Stroke	0.70	(Hirose, et al., 2009)
	Mediastinitis * Prolonged hospital stay * Prolonged ventilation * Renal failure * Return to theatre * Stroke	0.72	(Wang, et al., 2017)
	Deep sternal wound infection * Prolonged hospital stay * Prolonged ventilation * Renal failure * Return to theatre * Stroke	0.59	(Wang, et al., 2016)
EuroSCORE II	Mediastinitis * Prolonged hospital stay * Prolonged ventilation * Renal failure	0.72	(Wang, et al., 2017)
	Deep sternal wound infection * Prolonged hospital stay * Prolonged ventilation hours * Renal failure * Return to theatre * Stroke	0.61	(Wang, et al., 2016)

Table 5: Area under the curve for combined complications for each risk model

Cleveland Clinic score has a slightly better performance at predicting combined complications in a single centre study in Germany (AUC=0.69) (Geissler, et al., 2000). A study investigating morbidity amongst CABG patients found that Cleveland Clinic score has a good discriminant power for predicting postoperative decreased oxygen delivery and need for inotropic support after surgery (Scolletta, et al., 2004).

STS score seems to have a better predictive ability for combined postoperative complications (AUC=0.73) in New Zealand amongst mitral valve surgery patients (Wang, et al., 2017), compared to an earlier study in New Zealand for combined

CABG and valve patients (ACU=0.63) (Wang, et al., 2016). Amongst combined CABG and valve patients in New Zealand, STS score also appears to perform slightly better than EuroSCORE (AUC=0.59) and EuroSCORE II (AUC=0.61) (Wang, et al., 2016).

In a Finnish single centre study, EuroSCORE predicts combined complications moderately well (AUC=0.70) (Pitkänen, et al., 2000), with a similar performance in Japan (AUC=0.70) (Hirose, et al., 2009), and slightly better than in Germany (AUC=0.64) (Geissler, et al., 2000). Compared to these studies, EuroSCORE appears to have the best performance for predicting combined complications, however, in New Zealand amongst patients undergoing mitral valve surgery (AUC=0.72) (Wang, et al., 2017). In the same study in New Zealand, EuroSCORE II has a similar performance to EuroSCORE (AUC=0.72) (Wang, et al., 2017).

3.6. Discussion

In this review, five pre-operative risk stratification tools were found to be validated in various studies for predicting postoperative complications. These scores are Initial Parsonnet score, EuroSCORE and EuroSCORE II that were initially designed to predict 30-day mortality following cardiac surgery, and STS and Cleveland Clinic score that were initially designed to predict 30-day mortality and morbidity after cardiac surgery.

The newest risk score EuroSCORE II shows the best performance when predicting mediastinitis (Wang, et al., 2017), compared to other observed scores. EuroSCORE II was the only observed score validated for predicting postoperative dialysis (Biancari, et al., 2012), prolonged inotrope use (Biancari, et al., 2012) and acute respiratory distress syndrome (Wang, et al., 2014), and performed considerably well.

Although EuroSCORE was designed to predict mortality, the literature shows considerably good performance at EuroSCORE predicting prolonged ICU stay (Pitkänen, et al., 2000; Messaoudi, et al., 2009; Nilsson, et al., 2004), renal failure (Toumpoulis, et al., 2005; Hirose, et al., 2009; Wang, et al., 2017), prolonged ventilation (Wang, et al., 2017; Wang, et al., 2014), mediastinitis (Hirose, et al., 2009;

Wang, et al., 2017), congestive cardiac failure (Hirose, et al., 2009), pneumonia (Hirose, et al., 2009) and stroke (Hirose, et al., 2009; Wang, et al., 2014).

STS score shows a good performance when predicting renal failure (Wang, et al., 2017; Wang, et al., 2014; Borde, et al., 2013) and deep sternal wound infection (Borde, et al., 2013), outperforming other scores. STS score is shown to predict combined complications considerably well (Wang, et al., 2017).

However, Cleveland Clinic score was initially designed to predict both mortality and morbidity, but did not perform as well as the other scores. In the original study, the morbidities Cleveland Clinic score was developed to predict were stroke, low cardiac output, myocardial infarction, prolonged ventilation, serious infection and renal failure (Higgins, et al., 1992). Firstly, Cleveland Clinic score was validated at predicting individual complications only in three studies, and combined complications in one study, whereas other scores were validated more often. Secondly, even if the score is developed to predict both mortality and morbidity, usually validation studies only include mortality as an outcome. The problem of literature focusing on mortality only is a problem for all scores in general. So, in order to make conclusions about the ability of Cleveland Clinic score to predict postoperative complications, more validation studies are needed. However, Cleveland Clinic score is shown to have good performance when predicting renal failure (Wong, et al., 2015; Candela-Toha, et al., 2008), but moderate performance when predicting combined complications (Geissler, et al., 2000), and is outperformed by the other risk scores.

Initial Parsonnet score is shown to have moderate performance when predicting prolonged ICU stay (Lawrence, et al., 2000), hospital length of stay (Syed, et al., 2004) and combined complications (Gabrielle, et al., 1997; Dupuis, et al., 2001; Syed, et al., 2004), but is outperformed by the other risk scores.

All scores include age, left ventricular function, pulmonary disease, previous cardiac surgery, type of surgery and surgical priority variables. Based on variables, the risk scores included in the review designed to predict mortality only differ from the risk scores, predicting both mortality and morbidity, by not including peripheral vascular disease variable. When it comes to the performance of the scores predicting specific complications, the models developed to predict mortality perform as well as the scores designed to predict mortality and morbidity, in some cases even better. When comparing the performance in predicting combined complications, all scores predict combined complications with a similar ability.

All scores include variables that are pre-operatively available, however some include more variables than others and therefore could be more time-consuming to calculate. In order to make calculations easier for clinicians, the developers of the scores have created online calculators for EuroSCORE, EuroSCORE II, and for STS score, explaining the popularity of the scores, especially for EuroSCORE and EuroSCORE II. The Initial Parsonnet score and Cleveland Clinic score do not have an online calculator, which might explain the lack of validation for predicting postoperative complications in the literature.

The amount of studies which EuroSCORE has been validated in can offer some certainty on the predictive ability of complications in various populations. Although STS score and EuroSCORE II have been included in smaller number of studies, they have been investigated at predicting many various severe complications, performing considerably well in most cases. There is less certainty about the performance of Initial Parsonnet score and Cleveland Clinic score due to not being investigated at predicting different complications.

The most analysed individual postoperative complications include renal failure, prolonged ventilation, ICU length of stay, mediastinitis and deep sternal wound infection. Various combined complications were often analysed, including stroke, myocardial infarction, bleeding, renal failure, mediastinitis and prolonged ventilation. These complications are all shown to have a significant impact on patient's quality of life, increased healthcare costs and mortality (Hogue, et al., 1999; Chen, et al., 2007; Ruel, et al., 2017; Jose Olivero, et al., 2012; Diez, et al., 2007; Trouillet, et al., 2009).

There are many various postoperative complications, and the definition of their severity can be subjective, depending on if focus is more on patients' quality of life after surgery or on healthcare costs. All studies included in the review have different outcomes: some have individual postoperative complications, some have combined complications. The variety of outcomes makes the validation of scores more difficult. On one hand, this problem could be solved by having a general agreement on which complications should be included in studies that are validating scores. On the other hand, populations have different postoperative complications, and different variables can have a different effect on the outcome, based on patient characteristics.

None of the observed risk scores perform particularly well at predicting combined complications. Although, the observed scores are good at predicting different certain postoperative complications, it would be unrealistic for a clinician to use different scores for each possible postoperative complication. For fast and efficient pre-operative risk assessment one score predicting combined severe complications is needed that could help improve patients' quality of life after surgery and decrease healthcare costs and long-term mortality.

In addition, the complications included as a combined outcome differed in each study, showing that there is no agreement, which complications should be included as a combined outcome.

In the UK the in-hospital mortality after cardiac surgery is considerably low, having stayed under 3% in the past five years (SCTS, 2014). The long-term mortality after cardiac surgery is analysed in the literature by Sharabiani, et al (long-term mortality of 38.9%) (Sharabiani, et al., 2016), Bernardi, et al. (long-term mortality of 53.5%) (Bernardi, et al., 2015), and Enger, et al. (long-term mortality of 23.9%) (Enger, et al., 2016), to name a few, but is not widely reported. To reduce long-term mortality, improve patients' quality of life, and decrease healthcare costs, postoperative complications need to be further investigated.

Different studies suggest, in order to make the score more relevant to the population, removing non-significant factors appropriate to the population can simplify the risk stratification (Chong, et al., 2003; Gabrielle, et al., 1997; Pitkänen, et al., 2000). Also, testing existing scores that predict mortality in predicting morbidity and long-term mortality can give a better understanding of the predicting ability of the score (Lawrence, et al., 2000; Collas, et al., 2016; Asimakopoulos, et al., 2003; Carnero-Alcazar, et al., 2013; Nilsson, et al., 2006). Every single study found in this review suggested that further validation and investigation in postoperative complications in different countries and institutions is needed.

Chapter Four: Methods

This work focuses on developing predictive models, using logistic regression and ordinal logistic regression. For each outcome, local prediction models were developed, and the performance of each local model was compared with the performance of logistic EuroSCORE predicting each outcome.

4.1. Setting

In Scotland, there are three hospitals that are specialised in cardiac surgery: Golden Jubilee National Hospital (GJNH), Royal Infirmary Edinburgh and Aberdeen Royal Infirmary, GJNH being the largest.

GJNH offers regional and national heart and lung services, orthopaedic services, and is the flagship hospital for reducing waiting times in elective specialties, treating patients from all over Scotland. At the GJNH, there are approximately 230 patient beds, 4 cardiac catheterisation labs and 16 theatres. More than 1600 staff members and more than 100 volunteers work at the GJNH. (Golden Jubilee National Hospital, 2016)

On average, Golden Jubilee National Hospital (GJNH) carries out 5241 elective heart surgeries per year, 591 of them being coronary artery bypass graft surgeries, 428 of them being valve procedures, and the rest being coronary angioplasties, arrhythmia and other heart procedures. The valve surgeries at GJNH make up 45.5%, and bypass surgeries make up 53.8% of all elective valve and bypass surgeries in NHS Scotland. (ISD Scotland, 2016)

4.2. Databases

The data for the analysis was extracted from two databases: Cardiac, Cardiology and Thoracic Health Information (CaTHI) System and WardWatcher.

The data about cardiac procedures in the Golden Jubilee National Hospital was obtained from CaTHI database, which has been developed at the Golden Jubilee National Hospital (GJNH, 2012). The database consists of cardiac, cardiology and thoracic patients' diagnostic assessments, surgical procedures and discharge information.

Golden Jubilee National Hospital started using CaTHI database in 2012, and therefore all admissions in cardiac surgery between 1st April 2012 and 31st March 2016 in Golden Jubilee National Hospital were recorded, adding up to 3838 admissions. All patients reported in CaTHI database had a cardiac procedure.

The intensive care unit (ICU) data was extracted from the WardWatcher database in order to gain information on the APACHE II score for each patient. The WardWatcher system includes data from all general adult ICUs, combined units and the majority of high dependency units (HDUs) (SICSAG, 2012). All admissions to the ICU after cardiac surgery between 1st April 2012 and 31st March 2016 were recorded at the Golden Jubilee National Hospital, adding up to 3792 admissions.

4.3. Data security and linkage

In order to access the databases, the student signed an honorary contract with the Golden Jubilee National Hospital which provided a read-only access to the student under the supervision of Cardiac Audit Data Manager.

The Ethics Committee of the Golden Jubilee Research Institute was contacted about the ethics approval. Due to the student working with anonymous data which is stored in an encrypted environment, and due to not having any patient contact, according to the Ethics Committee the review and approval was not required.

The data from the CaTHI and WardWatcher database were linked by the Department of eHealth at the Golden Jubilee National Hospital, using Community Health Index (CHI), which was replaced with an anonymous patient identifier before the analysis.

Patients undergoing coronary artery bypass graft (CABG), valve surgery, or combined CABG and valve surgery who had an APACHE II score evaluated were included in the study. The list of exact procedures can be found from Appendix A.

4.4. Variables and missing data

The linked data consisted of 25 variables, which can be found from Appendix A. The predictors included patient characteristics, pre-operative variables about patients' cardiac status and co-morbidities, variables about surgery, and pre-operatively calculated logistic EuroSCORE, recorded in CaTHI database.

Golden Jubilee National Hospital uses logistic EuroSCORE in order to assess risk of mortality amongst cardiac patients, and therefore the logistic EuroSCORE variables are mandatory fields in CaTHI database. Hence, there were no missing data for logistic EuroSCORE variables (Table 5).

Patient characteristics	**Non-cardiac variables**
Age	Pulmonary disease
Sex	Neurological dysfunction
Cardiac variables	Creatinine > 200μmol/L
Extracardiac arteriopathy	**Surgery**
Active endocarditis	Surgical priority
Unstable angina	Procedure
LV function	Critical preoperative state
Previous MI	Previous cardiac surgery
Hypertension history	

Table 5: Mandatory variables included in CaTHI database i.e. Logistic EuroSCORE variables, where LV – left ventricular, MI – myocardial infarction

However, CaTHI also includes some non-mandatory fields, some of which are also consistently filled in. These variables are diabetes, NYHA grade, BMI and congestive cardiac failure. The completeness of variables is also included in Appendix B.

Some variables, not included in logistic EuroSCORE, were considerably consistently filled in. In that case, the blank fields for categorical variables were coded as "Unknown". The variables with "Unknown" entries included renal impairment (43.38% unknown), rhythm (7.97%), smoking status (36.24%), and left main stem (LMS) (48.76%).

If the continuous variable was not filled in consistently, the variable was excluded from the analysis. The only variable excluded from the analysis due to that reason was preoperative haemoglobin level.

Some of the variables had inconsistencies in the units reported. For example, some results for the body mass index (BMI) were unrealistic due to the height being recorded in imperial units, instead of metric units. These inconsistencies were discussed with the Cardiac Audit Data Manager and fixed accordingly by changing the units as appropriate.

4.5. Model development

The CaTHI database reports various postoperative variables, including mortality, hospital length of stay, ICU length of stay and if the patient had any postoperative complications.

This project focuses on three outcomes associated with postoperative complications:

- Model 1: Postoperative complication (yes/no)
- Model 2: Severe postoperative complication (yes/other complication or no complication)
- Model 3: Level of complication (no/mild/moderate/severe)

For Model 2 and 3, the complications were divided into four groups based on the effect on hospital length of stay, long-term effects on patient's quality of life, and cost of care, based on the evidence in literature and the opinion of Stefan Schraag, the Professor of Anaesthesia at the Golden Jubilee National Hospital. The criteria for each complication level are as follows:

- No complication – no complication recorded after surgery
- Mild complication – complication that is easily treated and does not have an effect on patient's quality of life, hospital length of stay or health care costs
- Moderate complication – complication that could significantly increase the hospital length of stay and increase health care hosts, but does not have a significant effect on patient's quality of life after surgery
- Severe complication – complication that could lead to death, significantly increase hospital length of stay, increase health care costs and has a significant effect on patient's quality of life.

The grouping of all complications listed in data can be found from Appendix C.

If a patient has more than one complication, then the patient was considered to have the highest level of complication that was recorded for them. For example, if a patient had two mild complications and one moderate complication, then the patient was considered to have a moderate complication in the analysis. More examples can be found from Table 6.

Patient ID	Complication 1	Complication 2	Complication 3	Complication level used in analysis
1	Mild	Severe		Severe
2	Moderate	Mild	Moderate	Moderate
3	Severe	Moderate		Severe
4	Mild			Mild

Table 6: Example of complication levels were obtained for each patient for analysis

4.6. Statistical analysis methods

For the analysis, the statistical package R is used. Twenty-five variables (see Appendix B) are investigated in order to find significant factors associated with the outcomes.

4.6.1. Logistic regression

Logistic regression is a widely used statistical modelling approach that is used to describe the relationship of independent variables to a dichotomous dependent variable. In this project the dichotomous variable is if the patient has postoperative complications (Yes/No) for Model 1, and if the patient has severe postoperative complications (Yes/Other or no complication) for the Model 2.

The logistic function $f(z) = \frac{1}{1+e^{-z}}$ ranges between 0 and 1, and therefore logistic mode is set up to ensure that any estimate of risk also ranges between 0 and 1. It is often the first choice when a probability is to be estimated, which is always a number between 0 and 1.

To obtain the logistic model, let z to be a linear sum, where $z = \alpha + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_k X_k$, where Xs are independent variables and α and β_i are constant terms representing unknown parameters. Then the logistic function becomes $f(z) = \frac{1}{(1+e^{-z})} = \frac{1}{1+e^{-(\alpha+\sum \beta_i X_i)}}$. Using the Model 1 outcome, we denote 1 as "with complication" and 0 as "without complication". In that case the probability of patient having a complication can be stated as $P(D = 1|X_1, X_2, \dots, X_k) = P(X)$. The logistic model is defined if the expression for the probability of having postoperative complication, given the Xs, is $P(X) = \frac{1}{1+e^{-(\alpha+\sum \beta_i X_i)}}$. (Kleinbaum & Klein, 2010)

When using the Model 1 outcome, we denote 1 as "with severe complication" and 0 as "with other or no complication", and the same processes follow for the two models.

Generalised linear model

In order to build logistic regression models, generalised linear model (GLM) is used. In this case the response variable is assumed to follow an exponential family distribution with mean μ, which is assumed to be some function of βX_i.

There are three components to any GLM:

- Random component – based on the probability distribution of the response variable, e.g. binomial distribution for postoperative complications in the binary logistic regression.
- Systematic component – specifies the linear combination of independent variables $(X_1, X_2, \ldots, X_k)$ in the model in creating the linear predictor, e.g. $\alpha + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_i X_k$.
- Link function – specifies the link between random and systematic components and how the expected value of the response relates to the linear predictor of independent variables, e.g. for logistic regression $\eta = \log\left(\frac{\pi}{1-\pi}\right)$.

(Dobson & Barnett, 2008)

Generalised additive model

For three continuous variables (age, body mass index (BMI), logistic EuroSCORE) generalised additive model (GAM) is used in order to visualise the association between the independent variable and the outcome.

By replacing the linear functions in GLM with non-parametric smooth functions, GAM is obtained. In order to achieve smoothness, splines are used. A spline is a numeric function that is piecewise-defined by polynomial functions, and which has a high degree of smoothness at the places where polynomial pieces connect, which are known as knots (A Dictionary of Statistics, 2014).

The standard linear regression model assumes that the expected value of Y has a linear form $E(Y) = f(X_1, \ldots, X_k) = \alpha + \beta_1 X_1 + \cdots + \beta_k X_k$, where Y is a response random variable and $X_1, \ldots, X_k$ is a set of predictor variables. The additive model generalises the linear model by modelling the expected value of Y as $E(Y) = f(X_1, \ldots, X_k) = s_0 +$

$s_1(X_1) + \cdots + s_k(X_k)$, where $s_i(X), i = 1, \ldots, k$ are smooth functions which are estimated in a nonparametric way. (Hastie & Tibshirani, 1990)

The GAM consists of three components:

- Random component, which is assumed to have a density in the exponential family $f_Y(y; \theta, \varphi) = \exp(\frac{y\theta - b(\theta)}{\alpha(\varphi)} + c(y, \varphi))$, where θ is the natural parameter and φ is the scale parameter.
- Additive component, which is defined by $\eta = s_0 + \sum_{i=1}^{k} s_i(X_i)$, where $s_1(.), \ldots, s_k(.)$ are smooth functions.
- Link function, which is defined by $g(\mu) = \eta$, where μ is the mean of the response variable.

(Hastie & Tibshirani, 1990)

It should be noted that the GAM was not used in the prediction model and was used for illustrative purposes only.

Unadjusted and adjusted odds ratios

The odds ratio (OR) is the only measure of association directly estimated from a logistic model. If we have a gender variable with male (M) and female (F), then given a logistic model of the general form $P(X)$, we can write the odds for male as $\frac{P(X_M)}{1-P(X_M)} = e^{(\alpha + \sum \beta X_M)}$, and for female as $\frac{P(X_F)}{1-P(X_F)} = e^{(\alpha + \sum \beta X_F)}$.

To calculate an odds ratio for female compared to male, we obtain $OR_{F,M} = \frac{e^{(\alpha + \sum \beta X_F)}}{e^{(\alpha + \sum \beta X_M)}} = e^{\sum \beta (X_F - X_M)} = e^{\beta}$, where e^{β} is the coefficient of gender variable in logit $P(X) = \alpha + \beta$ Gender. As in this case the gender variable is the only variable in the model, the odds ratio calculated is an unadjusted odds ratio. (Kleinbaum & Klein, 2010)

If we have three variables, gender, age and body mass index (BMI), and the logistic regression model is logit $P(X) = \alpha + \beta_1\text{Gender} + \beta_2\text{Age} + \beta_3\text{BMI}$, then the adjusted odds ratio for female compared to male of having postoperative complications is

$OR_{F,M} = e^{\beta_1}$, and the age and BMI variables are treated as control variables. (Kleinbaum & Klein, 2010)

Model development and measuring performance

In order to develop the prediction model and measure its performance, the dataset is randomly split into two: train data, that has 2/3 of the entries, and test data, that has 1/3 of the entries. The training set is used to fit the model, using forward selection. Forward selection starts with no predictors in the model, and significant variables are added to the model step by step. The model will include all variables that are significant on 95% significance level (p-value < 0.05) based on training data. The statistically insignificant variables were excluded from the model.

The performance of the model is measured with receiver operating characteristic (ROC) curve, using test data. An ROC curve is a graphical representation of the arrangement between the false negative and false positive rates for every possible cut off. The position of the cut-off determines the number of true positive, true negative, false positive and false negative outcomes. (Roos, et al., 1997)

The area under the curve (AUC), also known as index of accuracy, or concordance index, is a traditional performance metric for a ROC curve. The AUC ranges from 0 to 1, the model having a better prediction power when AUC is closer to 1. For example, AUC=0.80 means that a randomly selected patient from the positive group has a test value larger than that for a randomly chosen patient from the negative group 80% of the time. (Agresti, 2007)

In addition to AUC, other performance measures are considered: sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

Sensitivity, also called the true positive rate, is the ability of a test to identify an individual as “diseased” correctly (Parikh, et al., 2008). Sensitivity can be calculated as shown by equation (1) (Powers, 2011).

$$Sensitivity = \frac{Number\ of\ true\ positives}{Number\ of\ true\ positives + Number\ of\ false\ negatives} = \\ = \frac{Number\ of\ true\ positives}{Total\ number\ of\ sick\ individuals\ in\ population} \tag{1}$$

Specificity, also called the true negative rate, is the ability of a test to identify an individual as “disease-free” correctly (Parikh, et al., 2008). Specificity can be calculated as shown by equation (2) (Powers, 2011).

$$Specificity = \frac{Number\ of\ true\ negatives}{Number\ of\ true\ negatives + Number\ of\ false\ positives} = \\ = \frac{Number\ of\ true\ negatives}{Total\ number\ of\ well\ individuals\ in\ population} \quad (2)$$

PPV shows the probability of patients actually having the disease when test is positive, and NPV shows the probability of patients actually being well when the test is negative. PPV and NPV can be calculated as shown by equations (3) and (4), respectively. (Powers, 2011)

$$PPV = \frac{True\ positive}{True\ positive + False\ positive} = \\ = Probability(Patient\ having\ disease\ when\ test\ is\ positive) \quad (3)$$

$$NPV = \frac{True\ negative}{False\ negative + True\ negative} = \\ = Probability(Patient\ not\ having\ disease\ when\ test\ is\ negative) \quad (4)$$

PPV and NPV are influenced by the prevalence of disease in the population. If high prevalence setting is tested, patients are more likely to test positive when actually having a disease than in a population with low prevalence. However, PPV and NPV are also affected by sensitivity and specificity, meaning they can be also calculated as shown in equations (5) and (6), respectively. (Powers, 2011)

$$PPV = \frac{sensitivity \times prevalence}{sensitivity \times prevalence + (1 - specificity) \times (1 - prevalence)} \quad (5)$$

$$NPV = \frac{specificity \times (1 - prevalence)}{(1 - sensitivity) \times prevalence + specificity \times (1 - prevalence)} \quad (6)$$

Predicted probabilities

In addition to ROC curves, predicted probabilities are used for understanding the model performance. The predicted probabilities tell how likely it is that an observation belongs to the class that is coded as 1 (has a disease). For classification, a threshold is needed to be found. The predicted probability thresholds are connected to sensitivity and specificity of the model. Sensitivity denotes the fraction of positives that are correctly specifies for a given threshold, and specificity denotes the fraction of negatives that were correctly specified for a given threshold.

For finding the predicted probabilities of the model, *predict()* command was used. For finding the cut-off value for probabilities, *pROC* library was used, using *coords()* command. The function takes a “roc” object as first argument, on which the optimal cut-off is the threshold that maximises the distance to the identity line of the ROC curve. According to Youden’s J statistic, the cut-off value is chosen to maximise both sensitivity and specificity at the same time (Youden, 1950). (Robin, et al., 2011)

The histograms for predicted probabilities for having a complication and for not having a complication are produced for patients for whom the complication (for Model 1) or severe complication (for Model 2) is true. This helps to visualise the sensitivity and specificity of the model in order to see if the model can identify patients who have complications and who do not have complications.

4.6.2. Ordinal logistic regression

For our third model, where the complication level is predicted, ordinal logistic regression is used. In this case the ordinal response Y represents levels of complications (no, mild, moderate, severe).

For using ordinal logistic regression, it is assumed that the response variable behaves in an ordinal fashion, with respect to each predictor. For checking whether this assumption holds, estimating expected value of $X|Y=j(E(X|Y=j))$ could be calculated, where X is a discrete predictor, $P_{jx}=\Pr(Y=j|X=x)$ is the probability that $Y=j$ given $X=x$ that is dictated from the model being fitted. Then

$$\Pr(X=x|Y=j)=\frac{\Pr(Y=j|X=x)}{\Pr(Y=j)},$$

$$E(X|Y=j)=\frac{\sum_x xP_{jx}\Pr(X=x)}{\Pr(Y=j)}=Z_i, \tag{7}$$

and the expectation can be estimated by

$$\hat{E}(X|Y=j)=\sum_{x}\frac{x\hat{P}_{jx}f_x}{g_j}, \tag{8}$$

where $\hat{P}_{jx}$ denotes the estimate of P_{jx} from the fitted one-predictor model, f_x is the frequency of $X=x$ in the sample of size n, and g_j is the frequency of $Y=j$ in the sample. (Harrell, Jr, 2001)

In this project, proportional odds model is used for ordinal logistic regression. The proportional odds model is stated as follows:

$$\Pr[Y\geq j|X]=\frac{1}{1+\exp\left[-\left(\alpha_j+X\beta\right)\right]}, \tag{9}$$

where $j=1,2,\dots,k$, which are the levels of the response variable. There are k intercepts (αs) and the regression coefficients β connect probabilities for varying j. (Harrell, Jr, 2001)

The assumptions for the proportional odds model are the following:

- The regression coefficients β are independent of j, the levels of the response variable.
- There is no $X\times Y$ interaction if the model holds.
- The log odds that $Y\geq j$ is linearly related to each X.
- There is no interaction between the Xs.

(Harrell, Jr, 2001)

The proportional odds model is interpreted, using odds ratios. An odds ratio is assumed to apply equally to all events $Y\geq j$, $j=1,2,\dots,k$. The $X_m+1{:}\,X_m$ odds ratio for $Y\geq j$ is e^{β_m}, for any cut-off j. (Harrell, Jr, 2001)

Another way to interpret ordinal regression results, is using predicted probabilities. In this case, the predicted probability for being each class – none, mild, moderate, severe – are found. The predicted probabilities for $Y\geq j$, $j=1,2,\dots,k$ can be calculated as follows:

$$\hat{P}_{ij}=\frac{1}{1+\exp[-(\hat{\alpha}_j+X_i\hat{\beta})]}, \tag{10}$$

where X_i stands for a vector of predictors for subject i (Harrell, Jr, 2001).

Model development and measuring performance

Similarly to the prediction models, where logistic regression is used, the model using ordinal regression is developed based on training data (2/3 of the data), using forward selection, and the performance is measured using test data (1/3 of the data). In this case, ordinal regression is four-dimensional and therefore the model accuracy and other performance measures are calculated based on a confusion matrix. A confusion matrix, or error matrix, is a table layout that visualises the performance of an algorithm, where each column represents the instances in a predicted class and each row represents the instances in an actual class, or vice versa (Powers, 2011).

For example, let us have a sample of 30 patients, 2 with severe, 10 with moderate, 6 with mild and 12 with no complications. Say, the confusion matrix looks like shown in Table 7.

		Predicted			
		No	Mild	Moderate	Severe
True	No	8	1	2	1
	Mild	1	3	2	0
	Moderate	3	0	7	0
	Severe	1	0	0	1

Table 7: An example of a confusion matrix, where the sample of 30 patients has 2 with severe, 10 with moderate, 6 with mild and 12 with no complications

In this example, the model predicted that 13 patients did not have complications, 4 had mild, 11 had moderate and 2 had severe complications. Based on the confusion matrix, for the patients who do not have complications, there are:

- 8 true positives (no complication correctly identified as no complication)
- 4 false positives (other complication levels incorrectly identified as no complication)
- 4 false negatives (no complication incorrectly identified as other complication levels)
- 13 true negatives (other complication levels correctly identified as not no complication).

Similarly to logistic regression, the sensitivity, specificity, PPV and NPV are calculated as shown in equations (1) to (4).

Another measure used to measure model performance, is accuracy, which shows the proportion of correct guesses. According to some, accuracy is not a reliable measure for the real performance of a classifier due to being affected by unbalanced datasets (Fawcett, 2006). For example, if there were 100 patients with moderate complications and 2 patients with severe complications, the accuracy could be biased into classifying all the samples as patients with moderate complications. The accuracy is calculated as follows:

$$Accuracy = \frac{True\ positives + True\ negatives}{Condition\ positive + Condition\ negative}. \tag{11}$$

(Fawcett, 2006)

Predicted probabilities and latent variables

For finding the cut-off terms to estimate the probability that the Y can take a particular value, we calculate the following:

$$P(Y = mild) = \frac{1}{1 + \exp(Z_i - \kappa_{mild})} \tag{12}$$

$$P(Y = moderate) = \frac{1}{1 + \exp(Z_i - \kappa_{moderate})} - \frac{1}{1 + \exp(Z_i - \kappa_{mild})} \tag{13}$$

$$P(Y = severe) = 1 - \frac{1}{1 + \exp(Z_i - \kappa_{moderate})} \tag{14}$$

Here Y is the level of complication (no/mild/moderate/severe), Z_i is the estimates for each level of complication, and κ is the threshold point for the continuous latent variable Y^*.

For example, if the threshold parameters of the model are 16.4 and 18.1, the values of Y are the following:

$$Y_i = mild \text{ if } Y^* \leq 16.4 \tag{15}$$

$$Y_i = moderate \text{ if } 16.4 \leq Y^* \leq 18.1 \#(14)$$

$$Y_i = severe \text{ if } Y^* \geq 18.1 \quad (16)$$

(Williams, 2015)

4.6.3. Comparison with logistic EuroSCORE

Using logistic EuroSCORE reported in CaTHI database, the same outcomes are considered as for locally developed models:

- Model 1: postoperative complication (yes/no)
- Model 2: severe postoperative complication (yes/other or no complication)
- Model 3: level of postoperative complication (no/mild/moderate/severe).

Similarly to local models, Model 1 and Model 2 are developed, using logistic regression, and Model 3 is developed, using ordinal logistic regression. In all cases, logistic EuroSCORE is the only variable in the model.

The performance is measured in the same fashion as for local models, in order to being able to compare the locally developed model and the performance of logistic EuroSCORE.

Chapter Five: Study population

5.1. Patient characteristics

In the final analysis, 3700 admissions were analysed, including 3628 unique patients undergoing coronary artery bypass graft (CABG) (59.65%), valve (26.49%), or combined CABG and valve (13.86%) surgeries.

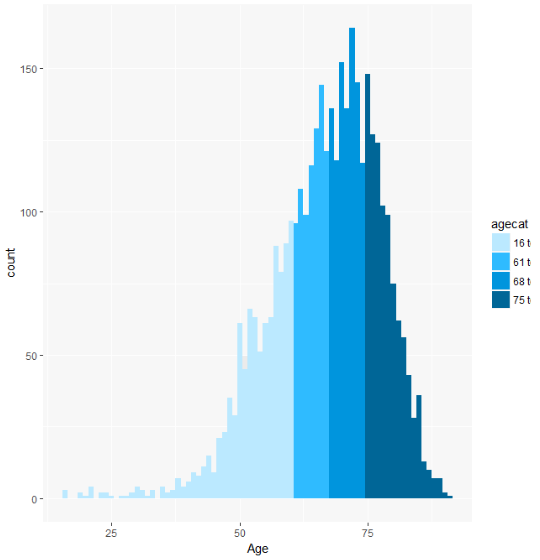

Figure 2: Histogram for age, with age categories used in analysis, where age categories are 16 to 60, 61 to 67, 68 to 74 and 75 to 99.

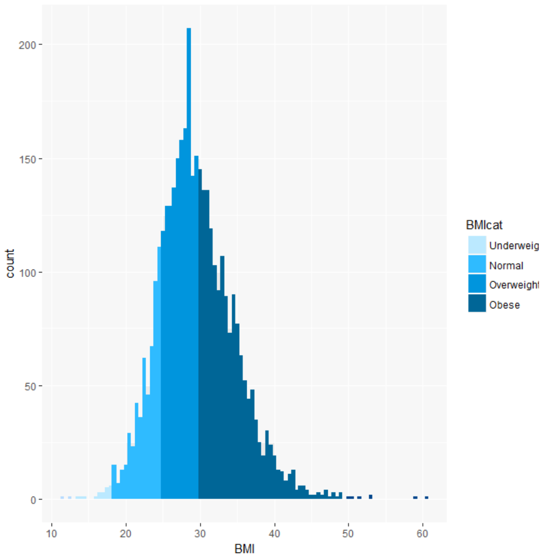

Figure 3: Histogram for body mass index (BMI), with BMI categories used in analysis, where BMI categories are "Underweight", "Normal", "Overweight" and "Obese".

The mean age of treated patients was 66.67, with the range of 16 to 91 years, and median of 68.00, the distribution of age being visualised in Figure 2. From Table 8 it can be seen that the patients were divided into four age groups: 16 to 60, 61 to 67, 68 to 74, and 75 to 99 year olds in order to achieve groups in similar sizes. The majority of the patients were male, with only 26.78% of them being female. Slightly more than a quarter of the patients (26.51%) had diabetes. Based on body mass index (BMI), the majority of the patients were obese (42.46%), 40.22% were overweight, 16.47% had a normal weight and 0.85% were underweight. The distribution of the BMI can be seen in Figure 3. Slightly less than a quarter of the patients (22.71%) had never smoked, 11.70% were current smokers, 29.35% were ex-smokers and for 36.24% of the patients the smoking status was not reported.

Variable	Group	Cases (%)
Age group	16 to 60	979 (26.46)
	61 to 67	813 (21.97)
	68 to 74	968 (26.16)
	75 to 99	940 (25.41)
Sex	Female	991 (26.78)
	Male	2709 (73.21)
Diabetes	Yes	981 (26.51)
	No	2719 (73.49)
BMI	Underweight (<18.5)	31 (0.85)
	Normal (18.5-24.9)	609 (16.47)
	Overweight (25.0-29.9)	1488 (40.22)
	Obese (>30.0)	1571 (42.46)
Smoking status	Never smoked	840 (22.71)
	Current smoker	433 (11.70)
	Ex-smoker	1086 (29.35)
	Unknown	1341 (36.24)

Table 8: Patient characteristics, where cases are treated patients, BMI – body mass index,

5.2. Cardiac pre-operative variables

The Table 9 shows that 5.59% of the patients had a congestive cardiac failure in the past and 2.22% had it at admission. Of all admissions, 36.68% had had a previous myocardial infarction (MI) in the past. A minority (0.73%) of the patients had active endocarditis at the admission. The majority (73.14%) of the patients had hypertension history. Slightly more than a half of the patients (51.92%) had the New York Heart Association (NYHA) grade of II, about a quarter of them (27.30%) having the grade III and 2.62% had the grade IV. The most common angina status was II with 37.81%, 16.38% had grade III and 4.89% had grade IV. Slightly more than a quarter (27.38%) of the patients did not have angina at admission. Most of the patients had a sinus rhythm (83.51%), slightly less than a tenth (8.51%) had an abnormal rhythm and for 7.98% of the patients the rhythm was not reported. The majority of the patients (81.21%) had a good left ventricular function. When it comes to left ventricular (LV) function, 16.03% of the patients had a moderate and 2.76% had a poor LV function. Around two fifths of the patients (38.43%) did not have a left main stem (LMS) disease, and for almost a half of the patients (48.76%) the state of LMS was not recorded. Slightly more than a tenth of the patients (13.27%) had extracardiac arteriopathy.

Variable	Group	Cases (%)
Congestive cardiac failure	Past	207 (5.59)
	At admission	82 (2.22)
	Never	3411 (92.19)
Previous MI	Yes	1357 (36.68)
	No	2343 (63.32)
Active endocarditis	Yes	27 (0.73)
	No	3673 (99.27)
Hypertension history	Yes	2706 (73.14)
	No	994 (26.86)
NYHA grade	I – No limitation of physical activity	672 (18.16)
	II – Slight limitation of ordinary physical activity	1921 (51.92)
	III – Marked limitation of ordinal physical activity	1010 (27.30)
	IV – Symptoms at rest or minimal activity	97 (2.62)
Angina status	0 – No angina	1013 (27.38)
	I – No limitation of physical activity	501 (13.54)
	II – Slight limitation of ordinary activity	1399 (37.81)
	III – Marked limitation of ordinary physical activity	606 (16.38)
	IV – Symptoms at rest or minimal activity	181 (4.89)
Rhythm	Sinus rhythm	3090 (83.51)
	Abnormal rhythm	315 (8.51)
	Unknown	295 (7.98)
LV function	Good (LVEF > 50%)	3005 (81.21)
	Moderate (LVEF 31-50%)	593 (16.03)
	Poor (LVEF < 30%)	102 (2.76)
LMS	No LMS disease or LMS disease ≤ 50% diameter stenosis	1422 (38.43)
	LMS > 50% diameter stenosis	474 (12.81)
	Unknown	1804 (48.76)
Extracardiac arteriopathy	Yes	491 (13.27)
	No	3209 (86.73)

Table 9: Descriptive statistics for cardiac pre-operative variables, where MI – myocardial infarction, NYHA – New York Heart Association, LV – left ventricular, LVEF – left ventricular ejection fraction, LMS – left main stem

5.3. Non-cardiac pre-operative variables

Table 10 shows that 2.14% the patients had neurological dysfunction and slightly less than a fifth of the patients (18.86%) had a pulmonary disease. A minority (0.86%) of the patients had the pre-operative serum creatinine 200µmol/L or higher. Slightly less than a third of the patients (31.59%) had a normal renal function, exactly a fifth (20.00%) having a moderate renal function, and 5.03% severely impaired renal function. For 43.38% of the patients the renal function was not reported.

Variable	**Group**	**Cases (%)**
Neurological dysfunction	Yes	79 (2.14)
	No	3621 (97.86)
Pulmonary disease	Yes	698 (18.86)
	No	3002 (81.14)
Pre. Op. creatinine (µmol/L)	< 200	3668 (99.14)
	≥ 200	32 (0.86)
Renal impairment	Normal renal function	1169 (31.59)
	Moderate impaired renal function	740 (20.00)
	Severely impaired renal function	186 (5.03)
	Unknown	1605 (43.38)

Table 10: Descriptive statistics for non-cardiac pre-operative variables

5.4. Surgical variables

From Table 11 it can be seen that the majority (77.54%) of the patients had an elective priority for the surgery. The 14.27% of the patients needed the surgery urgently, 7.49% were prioritised and 0.70% had an emergency surgery. A small group (1.14%) of patients were in a critical preoperative state. More than a half of the patients (59.65%) were undergoing CABG and slightly more than a fifth of the patients (26.49%) had a valve surgery. 13.86% of the patients had a combined CABG and valve surgery. The 2.51% of the patients had had a previous cardiac surgery before and slightly more than a tenth of the patients (13.00%) had had a previous percutaneous coronary intervention (PCI) before.

Variable	Group	Cases (%)
Surgical priority	Elective	2869 (77.54)
	Emergency	26 (0.70)
	Prioritised	277 (7.49)
	Urgent	528 (14.27)
Critical preoperative state	Yes	42 (1.14)
	No	3658 (98.86)
Procedure	CABG	2207 (59.65)
	Valve	980 (26.49)
	CABG and Valve	513 (13.86)
Previous cardiac surgery	Yes	93 (2.51)
	No	3607 (97.49)
Previous PCI	Yes	481 (13.0)
	No	3219 (87.0)

Table 11: Descriptive statistics for surgical variables, where PCI – percutaneous coronary intervention, CABG – coronary artery bypass graft

5.5. Other variables

Each patient had logistic EuroSCORE calculated before surgery. Table 12 shows that the mean logistic EuroSCORE was 5.13 and median 3.27. Having logistic EuroSCORE being higher than or equal to 20 (Arangalage, et al., 2014), 2.51% of the patients were considered to be high-risk patients. Figure 4 shows that the majority of the patients are low-risk patients according to logistic EuroSCORE being near zero, with 68% of the patients having the logistic EuroSCORE of 5 or less.

Variable	Group	Cases (%)
APACHE II score (mean, median, range)		15.23, 15 (0-44)
Logistic EuroSCORE (mean, median, range)		5.13, 3.27 (0.88-68.74)
Logistic EuroSCORE	<20 (low to medium risk)	3607 (97.49)
	≥ 20 (high risk)	93 (2.51)

Table 12: Descriptive statistics for other variables, where APACHE II – Acute Physiology and Chronic Health Evaluation II, EuroSCORE – European system for cardiac operative risk evaluation

Each patient had also APACHE II score calculated at the admission to the ICU. The mean APACHE II score was 15.23, median being 15, with the range of 0 to 44, which is also illustrated by Figure 5.

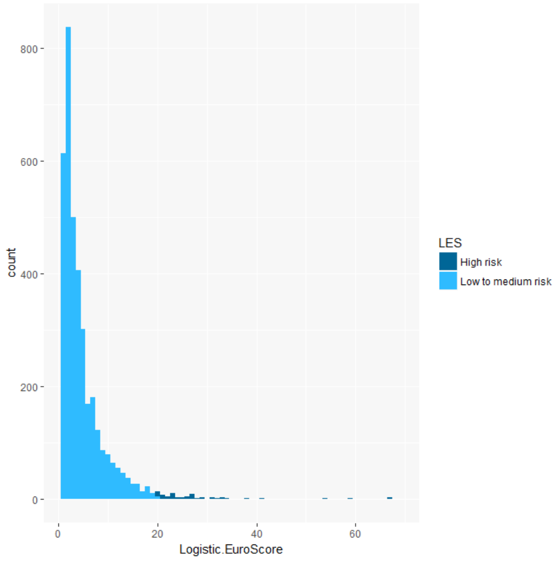

Figure 4: Histogram of logistic EuroSCORE

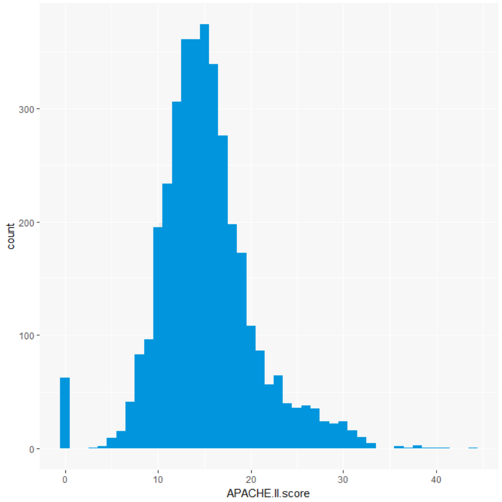

Figure 5: Histogram of APACHE II score

Chapter Six: Predicting postoperative complications

Of all admissions, 48.65% experienced postoperative complications. Overall, 78 different postoperative complications were recorded, the most prevalent being atrial fibrillation (28.41%, 95% CI 26.98-29.88%), the need for inotropes (13.73%, 95% CI 12.66-14.88%), the requirement of continuous positive airway pressure (CPAP) (8.97%, 95% CI 8.09-9.94%), the need to return to the theatre (5.19%, 95% CI 4.52-5.95%), and having a pulmonary infection requiring antibiotics (4.92%, 95% CI 4.27-5.66%). The occurrence of all complications and the classification of each complication into mild/moderate/severe can be found from Appendix C.

As slightly more than half (51.35%) of the patients did not have postoperative complications, the mean number of complications patients had was 1.003, median being 0, with the range of 0 to 17, which is visualised in Figure 7. As seen in Table 13, 25.78% of the patients have one complication, 11.90% have two complications and 10.97% have three or more compliations.

Variable	**Group**	**Cases (%)**
Number of complications	None	1900 (51.35)
	1	954 (25.78)
	2	440 (11.90)
	≥ 3	406 (10.97)

Table 13: Number of different postoperative complications each patient had after surgery

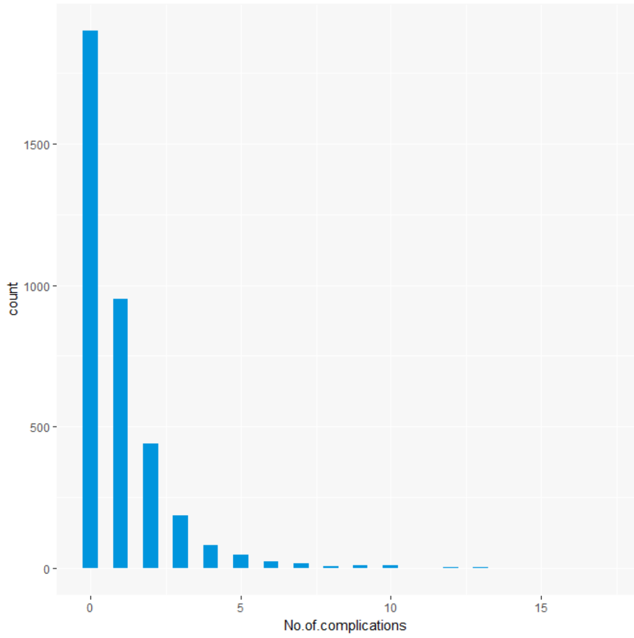

Figure 6: Histogram of number of complications after surgery

6.1. Variables associated with postoperative complications

Based on chi-square test of independence, the patient characteristics, cardiac pre-operative variables, non-cardiac pre-operative variables, and surgical variables found in Tables 14, 15, 17 and 18 were analysed. For all these variables unadjusted and adjusted odds ratios for having a complication were obtained in order to see which variables affect patients having postoperative complications. Here, the adjusted odds ratios represent the odds ratios obtained from combining all variables from Tables 14, 15, 17, 18.

	With complications	UNADJUSTED	ADJUSTED	
		OR (95% CI)	OR (95% CI)	P-value
Age: 16 to 60	36.5%	1.00	1.00	
Age: 61 to 67	49.0%	1.67 (1.38-2.02)	1.72 (1.41-2.09)	<0.001
Age: 68 to 74	52.1%	1.89 (1.58-2.27)	1.90 (1.56-2.30)	<0.001
Age: 75 to 99	57.6%	2.36 (1.97-2.84)	2.22 (1.79-2.76)	<0.001
Sex: Male	47.2%	1.00	1.00	
Sex: Female	52.6%	1.24 (1.07-1.43)	1.04 (0.88-1.22)	0.6690
Smoking Status: Never smoked	46.5%	1.00	1.00	
Smoking Status: Current smoker	44.8%	0.93 (0.74-1.18)	1.12 (0.87-1.44)	0.3847
Smoking Status: Ex-smoker	48.2%	1.07 (0.89-1.28)	1.11 (0.92-1.34)	0.2812
Smoking Status: Unknown	51.6%	1.22 (1.03-1.46)	1.24 (1.03-1.49)	0.0208

Table 14: Unadjusted and adjusted odds ratios for patient characteristics predicting postoperative complications, with 95% confidence intervals and P values

Postoperative complications seem more likely to be present with the higher age. Based on adjusted odds ratios from Table 14, patients aged 61-67 are 1.72 (95% CI 1.41-2.09) times more likely, aged 68 to 74 are 1.90 (95% CI 1.56-2.30) times and patients aged 75 to 99 are 2.22 (95% CI 1.79-2.76) times more likely to have postoperative complications than patients who are 60 years old or younger.

The increase of odds ratio with higher age can also be seen from Figure 7. The solid line on the figure shows the increase of odds ratios of patient having postoperative complications with increasing age. The 95% confidence intervals, visualised with the dotted line are wider at the ends of the figure due to smaller sample size amongst patients younger than 50 and older than 90. It should be noted, that the y-axis is on the GAM scale, and is not very interpretable. This is used for visualisation only.

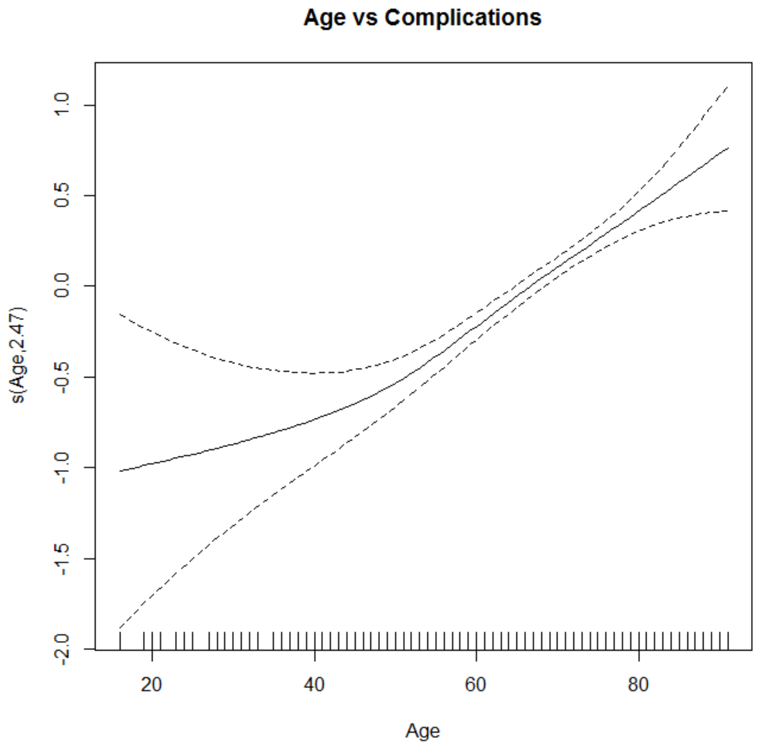

Figure 7: Age vs postoperative complications, using GAM, where the solid line is the odds ratios of patient having postoperative complication for each age group, and is bounded by 95% CI

The sex variable predicting postoperative complications on its own shows that female patients are more likely (OR=1.24, 95% CI 1.07-1.43) to have postoperative complications. However, based on adjusted odds ratios, the effect of sex variable diminishes (p=0.6690).

Although being a current smoker (p=0.3847) and ex-smoker (p=02812) are insignificant, patients with an unknown smoking status are 1.24 (95% CI 1.05-1.49) times more likely to have postoperative complications than patients who have never smoked.

From Table 15 it can be seen that based on unadjusted odds ratios, patients who have had congestive cardiac failure in the past are 1.67 (95% CI 1.26-2.23) times more likely to have postoperative complications than patients who have never had it. However, the effect of this variable diminishes, based on adjusted odds ratios (p=0.0797).

Based on adjusted odds ratios, patients who have had a myocardial infarction are 1.35 (95% CI 1.16-1.58) times more likely to have postoperative complications than patients who have never had a myocardial infarction. Although, NYHA Grade II (p=0.2058) and Grade III (p=0.0665) are insignificant based on adjusted odds ratios, having NYHA Grade IV, a patient is 1.85 (95% CI 1.14-3.04) times more likely to have postoperative complications than patients with no limitation of physical activity and have NYHA grade I. Having a poor LV function makes the patient 1.85 (95% CI 1.18-2.94) times more likely to have a postoperative complication than having a good LV function.

	With complications	UNADJUSTED	ADJUSTED	
		OR (95% CI)	OR (95% CI)	P-value
Congestive Cardiac Failure: Never	47.7%	1.00	1.00	
Congestive Cardiac Failure: Now	57.3%	1.47 (0.95-2.30)	0.91 (0.54-1.52)	0.7143
Congestive Cardiac Failure: Past	60.4%	1.67 (1.26-2.23)	1.32 (0.97-1.80)	0.0797
Previous MI: No	47.2%	1.00	1.00	
Previous MI: Yes	51.1%	1.17 (1.02-1.33)	1.35 (1.16-1.58)	0.0002
NYHA Grade: I - No limitation of physical activity	42.9%	1.00	1.00	
NYHA Grade: II - Slight limitation of ordinary physical activity	47.6%	1.21 (1.02-1.45)	1.13 (0.94-1.35)	0.2058
NYHA Grade: III - Marked limitation of ordinary physical activity	52.7%	1.48 (1.22-1.81)	1.22 (0.99-1.50)	0.0665
NYHA Grade: IV - Symptoms at rest or minimal activity	67.0%	2.71 (1.74-4.29)	1.85 (1.14-3.04)	0.0143
Rhythm: Sinus rhythm	49.7%	1.00	1.00	
Rhythm: Abnormal rhythm	41.3%	0.71 (0.56-0.90)	0.50 (0.39-0.64)	<0.001
Rhythm: Unknown	45.8%	0.85 (0.67-1.09)	0.75 (0.58-0.96)	0.0241
LV Function: Good (LVEF >50%)	47.9%	1.00	1.00	
LV Function: Moderate (LVEF 31-50%)	49.6%	1.07 (0.90-1.28)	0.97 (0.80-1.17)	0.7313
LV Function: Poor (LVEF <30%)	65.7%	2.08 (1.39-3.19)	1.85 (1.18-2.94)	0.0075

Table 15: Unadjusted and adjusted odds ratios for cardiac pre-operative variables predicting postoperative complications, with 95% confidence intervals and P values

Surprisingly, based on adjusted odds ratios, patients with an abnormal rhythm are less likely to have postoperative complications (OR=0.50, 95% CI 0.39-0.64) than patients with a sinus rhythm. This could be explained by the fact that the majority (83.51%) of the patients had sinus rhythm, and almost half (49.7%) of the patients with a sinus rhythm pre-operatively had postoperative complications. However, based on Table 16, 26.57% of the patients with sinus rhythm had one postoperative complication, 12.30% had two complications, and 10.81% had three or more complications. There can also be an association between the severity of complications and the pre-operative rhythm, which will be discussed in Section 8.1.

	No complications	1 complication	2 complications	3 or more complications
Rhythm				
Abnormal rhythm (%)	185 (58.73)	60 (19.05)	27 (8.57)	43 (13.65)
Sinus rhythm (%)	1555 (50.32)	821 (26.57)	38 (12.30)	334 (10.81)
Unknown (%)	160 (54.24)	73 (24.75)	33 (11.19)	29 (9.83)

Table 16: Number of complications based on pre-operative rhythm of the heart

Table 17 shows that the pulmonary disease variable gives a patient a higher risk of having postoperative complications based on unadjusted odds ratios (OR=1.18, 95% CI 1.00-1.39), however is insignificant based on adjusted odds ratios (p=0.3322).

Although, having moderate, severe and unknown renal function are significant risk factors on their own, based on adjusted odds ratios, only unknown renal function is significant when predicting postoperative complications. Patients whose renal function was not recorded are 1.31 (95% CI 1.11-1.54) times more likely to have complications than patients with a normal renal function.

	With complications	**UNADJUSTED**	**ADJUSTED**	
		OR (95% CI)	**OR (95% CI)**	**P-value**
Pulmonary disease: No	47.9%	1.00	1.00	
Pulmonary disease: Yes	52.0%	1.18 (1.00-1.39)	1.09 (0.92-1.30)	0.3322
Renal Impairment: Normal renal function	42.1%	1.00	1.00	
Renal Impairment: Moderate impaired renal function	49.7%	1.36 (1.13-1.64)	1.02 (0.84-1.25)	0.8185
Renal Impairment: Severely impaired renal function	56.5%	1.78 (1.31-2.44)	1.20 (0.86-1.69)	0.2808
Renal Impairment: Unknown	52.0%	1.49 (1.28-1.74)	1.31 (1.11-1.54)	0.0012

Table 17: Unadjusted and adjusted odds ratios for non-cardiac pre-operative variables predicting postoperative complications, with 95% CIs and P values

From Table 18 it can be seen that prioritised and urgent surgical priority are a significant risk factors for having postoperative complications on their own (OR=0.72 and OR=1.21, respectively), the adjusted odds ratios show that the surgical priority is an insignificant variable (p=0.0756 and p=0.2585, respectively).

Based on adjusted odds ratios, if the patient is at a critical pre-operative state at the time of admission, they are 2.30 (95% CI 1.10-5.18) times more likely to have complications than patients who are not at a critical state. Patients having an aortic valve surgery are 1.33 (95% CI 1.11-1.60) times more likely and patients having a combined aortic valve and CABG surgery are 1.52 (95% CI 1.22-1.88) times more likely to have postoperative complications than patients who are having a CABG surgery.

	With complications	UNADJUSTED	ADJUSTED	
		OR (95% CI)	OR (95% CI)	P-value
Priority: Elective	48.5%	1.00	1.00	
Priority: Emergency	57.7%	1.45 (0.67-3.24)	0.88 (0.37-2.13)	0.7815
Priority: Prioritised	40.4%	0.72 (0.56-0.92)	0.79 (0.61-1.02)	0.0756
Priority: Urgent	53.2%	1.21 (1.00-1.45)	1.13 (0.92-1.39)	0.2585
Critical Pre. Op. State: No	48.3%	1.00	1.00	
Critical Pre. Op. State: Yes	76.2%	3.42 (1.74-7.35)	2.30 (1.10-5.18)	0.0334
Procedure: CABG	44.9%	1.00	1.00	
Procedure: Valve	51.3%	1.29 (1.11-1.50)	1.33 (1.11-1.60)	0.0020
Procedure: Valve and CABG	59.5%	1.80 (1.48-2.19)	1.52 (1.22-1.88)	0.0001

Table 18: Unadjusted and adjusted odds ratios for surgical variables predicting postoperative complications, with 95% CIs and P values

6.2. Local model predicting postoperative complications

In the Section 6.1, the significant variables predicting postoperative complications were found: age, smoking status, previous MI, NYHA grade, rhythm, LV function, renal function, critical pre-operative state, and procedure.

The data was randomly divided into two: training data, including 2479 admissions, and testing data, including 1221 admissions.

Using the training data, the final model predicting postoperative complications, using logistic regression and forward selection, was developed:

$$Postoperative\ complication = \text{Yes} \sim Age + Previous\ MI + NYHA\ Grade + \\ + Rhythm + LV\ Function + Renal\ Impairment + \\ + Critical\ Pre\ Op.State + Procedure. \qquad (17)$$

The Table 18 shows the coefficients included in the model with estimate showing the amount by which the log odds of having postoperative complications would increase based on the level of the variable. The standard error (std. error), being associated with estimate, indicates how much on average the estimate would vary if the model would be run identically with new data. The z value is the result of estimate divided by the standard error. The p-value is the two-tailed p-values that correspond to the z values in a standard normal distribution.

For example, according to the estimate, patients aged 61 to 67 the log odds of having postoperative complications increase 0.5283 times, compared to patients aged 16 to 60. Based on standard error, the estimate of age 61 to 67 varies by 0.1216 on average, if using different data. The odds ratio for age group 61 to 67 is highly significant based on the p-value of p<0.001.

As it can be seen from Table 19, the variables included in the final prediction model are age, previous MI, NYHA grade IV, rhythm, poor LV function, renal impairment, critical pre-operative state, and procedure, all variables being significant as the p-value <0.05 on a 95% significance level.

Variable	Level	Estimate	Std. Error	z value	P-value	OR (95% CI)
(Intercept)		-0.9320	0.1406	-6.629	<0.001	
Age	16 to 60					1
	61 to 67	0.5283	0.1216	4.346	<0.001	1.70 (1.34-2.15)
	68 to 74	0.5969	0.1188	5.023	<0.001	1.82 (1.44-2.29)
	75 to 99	0.7383	0.1305	5.658	<0.001	2.09 (1.62-2.70)
Critical pre-op. state	No					1
	Yes	1.7992	0.6286	2.862	<0.001	6.04 (2.03-26.02)
Procedure	CABG					1
	Valve	0.1996	0.1093	1.826	<0.001	1.22 (0.99-1.51)
	Valve and CABG	0.3622	0.1336	2.712	0.0067	1.44 (1.11-1.87)
LV function	Good					1
	Moderate	0.0341	0.1169	0.292	0.7702	1.03 (0.82-1.30)
	Poor	0.8551	0.2996	2.854	0.0043	2.35 (1.33-4.32)
Renal Impairment	Normal renal function					1
	Moderate impaired renal function	0.0605	0.1236	0.489	0.6245	1.06 (0.83-1.35)
	Severely impaired renal function	0.3118	0.1999	1.560	0.1189	1.37 (0.92-2.03)
	Unknown	0.2170	0.0997	2.176	0.0296	1.24 (1.02-1.51)
NYHA grade	I					1
	II	0.0497	0.1130	0.440	0.6603	1.05 (0.84-1.31)
	III	0.2229	0.1276	1.747	0.0807	1.25 (0.97-1.61)
	IV	0.8660	0.3273	2.645	0.0082	2.38 (1.27-4.62)
Rhythm	Sinus					1
	Abnormal	-0.6688	0.1525	-4.386	<0.001	0.51 (0.38-0.69)
	Unknown	-0.1806	0.1585	-1.140	0.2545	0.83 (0.61-1.14)
Previous MI	No					1
	Yes	0.3137	0.0967	3.245	0.0012	1.37 (1.13-1.65)

Table 19: The prediction model with coefficients, their estimates, standard errors, z values, p values and odds ratios

A model with a high discrimination ability will have high sensitivity and specificity at the same time. Using the test data, the ROC curve (Figure 8) was produced, obtaining the area under the curve of 0.636 with the sensitivity of 65.7%, meaning that the model identifies patients with complications correctly 65.7% of the time. The specificity of 54.6% means that the model identifies patients with no complications correctly 54.6% of the time. The positive predictive value (PPV) of 37.1% shows that when the test is positive, the probability that patients actually have postoperative complications is 37.1%. The negative predictive value (NPV) of 42.4% means that when the test is negative, the probability of patients not having postoperative complications is 42.4%.

Although, the area under the curve shows a moderate discriminative ability for the model predicting patients with postoperative complications, the sensitivity is moderate, and specificity of the model is considerably low.

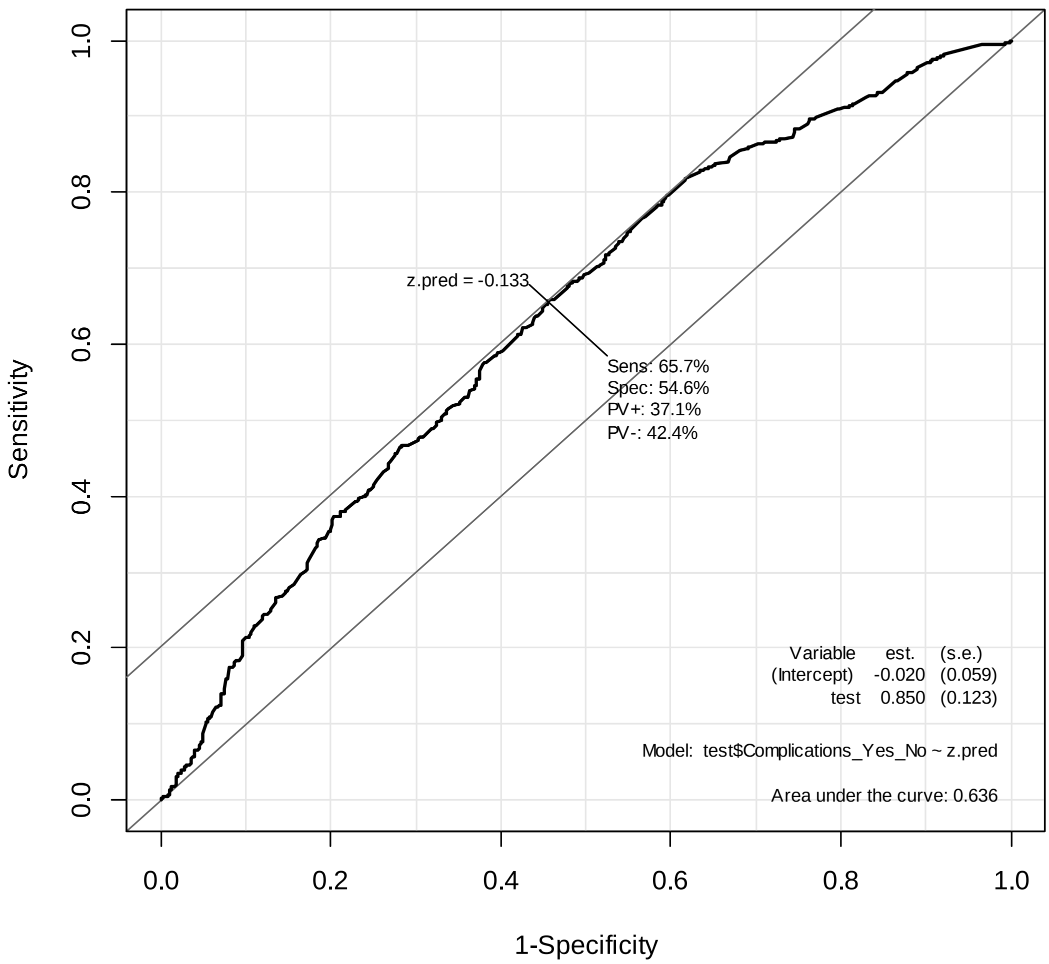

Figure 8: ROC curve for the locally developed model predicting postoperative complications, based on test data

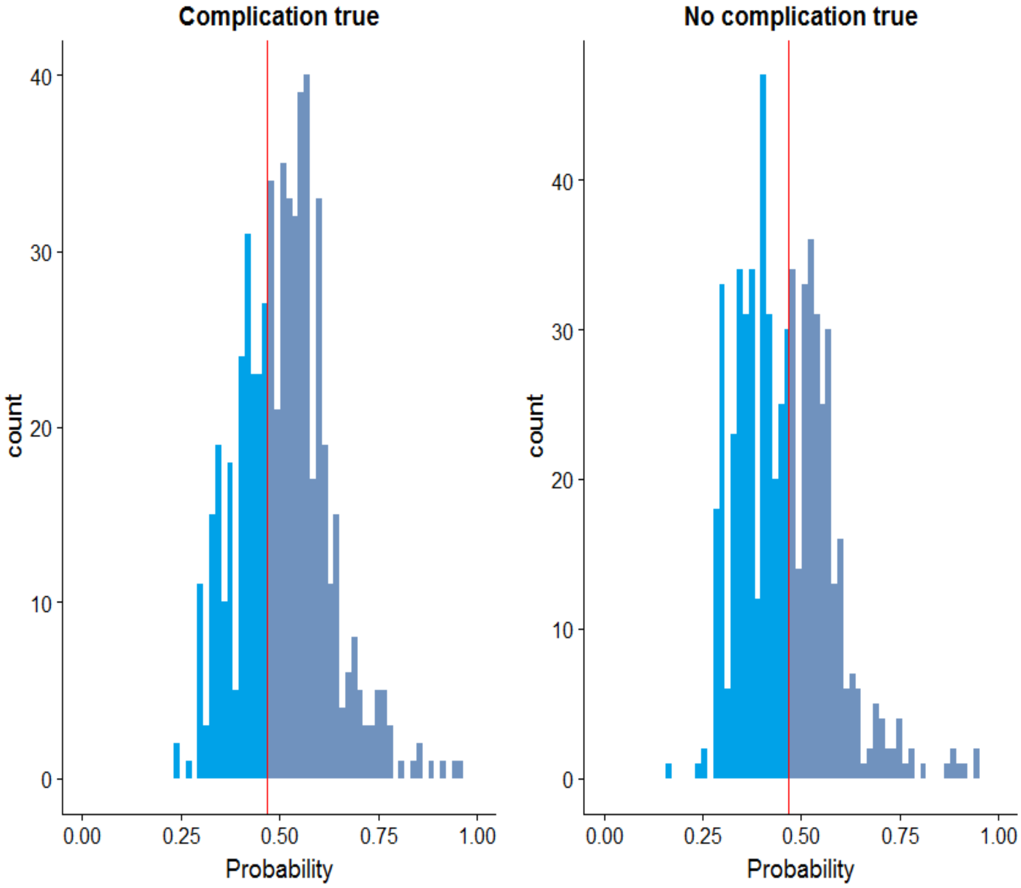

Figure 9: Predicted probabilities of a patient having postoperative complications, based on test data, if having a postoperative complication is true on the right, and if having no complication is true on the left. The red line indicates the threshold of 0.467, meaning that the predicted probabilities over the threshold indicate patients having postoperative complications according to the model.

Figure 9 shows the predicted probabilities of having a postoperative complications. The figure on the left shows patients for whom having a complication is true. More patients seem to have a predicted probability higher than the threshold of 0.467, meaning that model does identify patients with postoperative complications, however, many patients still have the predicted probability under the threshold, although they actually have a complication. This is also shown by the considerably low sensitivity.

The figure on the right shows the predicted probabilities for patients who actually do not have a postoperative complication. It can be seen that more patients have the predicted probability under the threshold of 0.467, indicating that the model can identify patients without complications. However, still a significant amount of patients have a predicted probability over the threshold. This is also described by the considerably low specificity.

6.3. Logistic EuroSCORE and postoperative complications

The Table 20 shows that logistic EuroSCORE is a significant risk factor for postoperative complications (p<0.001). Based on odds ratios, with every increasing unit of logistic EuroSCORE, the patient is 1.05 (95% CI 1.04-1.06) times more likely to have postoperative complications, compared to patients with a lower logistic EuroSCORE.

Variable	OR (95% CI)	P-value
Logistic EuroSCORE	1.05 (1.04-1.06)	<0.001

Table 20: Odds ratio for logistic EuroSCORE to show the association with postoperative complications with 95% CI and p value

High risk of mortality patients are also at risk for having postoperative complications. The Table 21 shows that patients with logistic EuroSCORE of 20 or higher are 2.15 (95% CI 1.40-3.37) times more likely to have postoperative complications than patients with logistic EuroSCORE less than 20.

Variable	Complications	OR (95% CI)	P-value
Logistic EuroSCORE < 20	46.97%	1.00	
Logistic EuroSCORE ≥ 20	1.68%	2.15 (1.40-3.37)	0.0006

Table 21: Odds ratios for logistic EuroSCORE predicting postoperative complications with 95% CIs and P values

Figure 10 shows that, using generalised additive model (GAM), the higher logistic EuroSCORE gives the patient a higher likelihood of having postoperative complications. However, the mean logistic EuroSCORE was 5.128 with the range of 0.88 to 68.74, meaning that the majority of patients have a relatively low logistic EuroSCORE, as seen in Figure 4 in Section 5.5. The wide range for confidence interval in Figure 10 indicates that we cannot be very certain about having postoperative complications when it comes to logistic EuroSCORE being higher than 20.

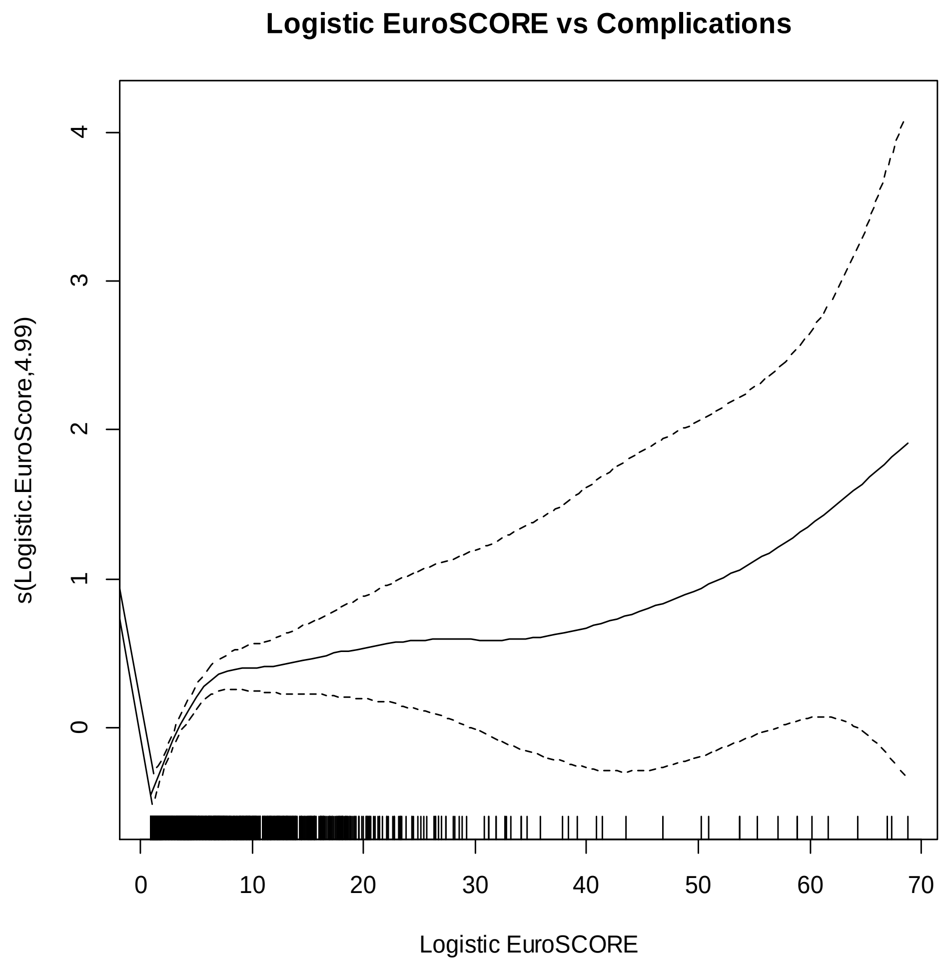

Figure 10: Logistic EuroSCORE vs postoperative complication using GAM. The solid line indicates odds ratios for each logistic EuroSCORE level, and is bounded by the 95% CI

6.3.1. Logistic EuroSCORE predicting postoperative complications

Using the training data, obtained in Section 6.2, the prediction model predicting postoperative complications was developed, using logistic regression and forward selection:

$$Postoperative\ complication = \text{Yes} \sim Logistic\ EuroSCORE \qquad (11)$$

	Estimate	Std. Error	z value	PP-value	OR (95% CI)
(Intercept)	-0.3033				
Logistic EuroSCORE	0.0498	0.0080	6.2060	<0.001	1.05 (1.04-1.07)

Table 22: Using logistic EuroSCORE as the only variable predicting postoperative complications, with its estimate, standard error, z value, p value and odds ratio with 95% CI

Table 22 shows that with every increasing unit of logistic EuroSCORE, the log odds of having postoperative complications increase 0.0498 times. According to standard error, on average the estimate would vary 0.008 times if the model would be run identically, but with different data. The two-tailed p-value <0.001 shows that the logistic EuroSCORE is a highly significant predictor for postoperative complications.

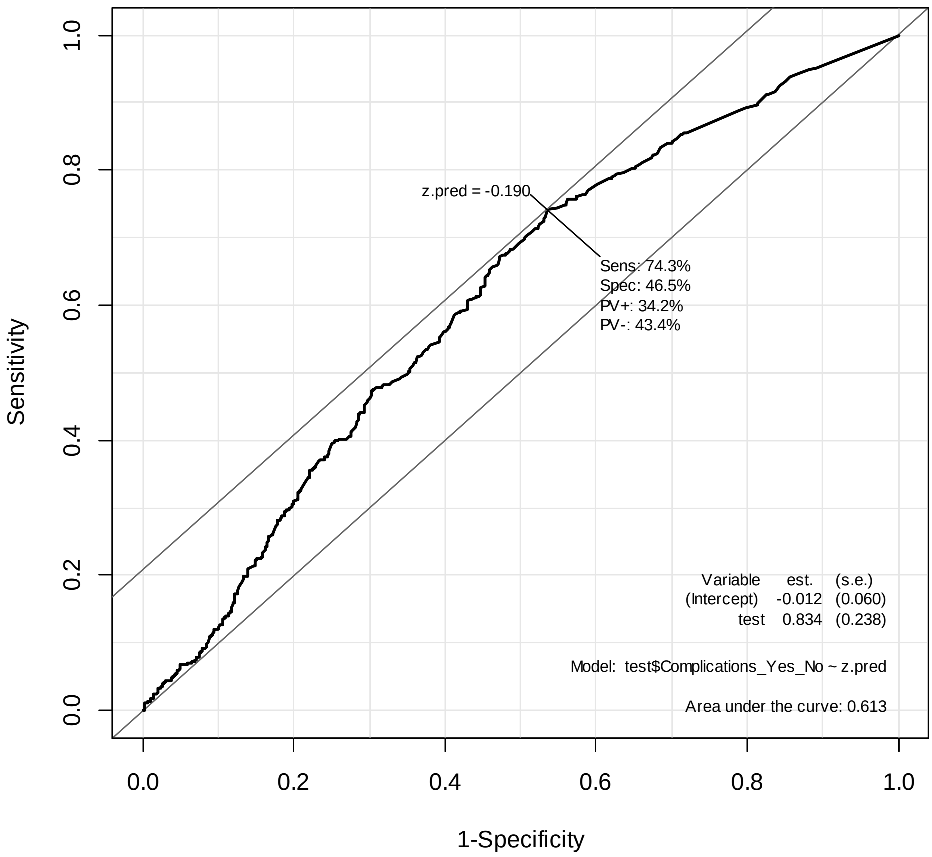

Figure 11: ROC curve of logistic EuroSCORE predicting postoperative complications, based on test data

In order to measure the performance level of the model, test data was used to obtain a ROC curve (Figure 11), resulting the area under the curve being 0.613. The sensitivity indicates that 74.3% of the time the model identifies patients with postoperative complications correctly. The specificity shows that the model identifies patients without postoperative complications 46.5% of the time correctly. This is an example, where specificity is lower at expense of sensitivity.

Based on the PPV, the probability of patient having a postoperative complication when the test is positive is 34.2%, and the NPV shows that when the test is negative, the probability of patient not having a postoperative complication is 43.4%. The considerably high sensitivity shows that the model can identify patients with postoperative complications. The relatively low NPV and higher PPV than for the local model are expected due to high prevalence of postoperative complications.

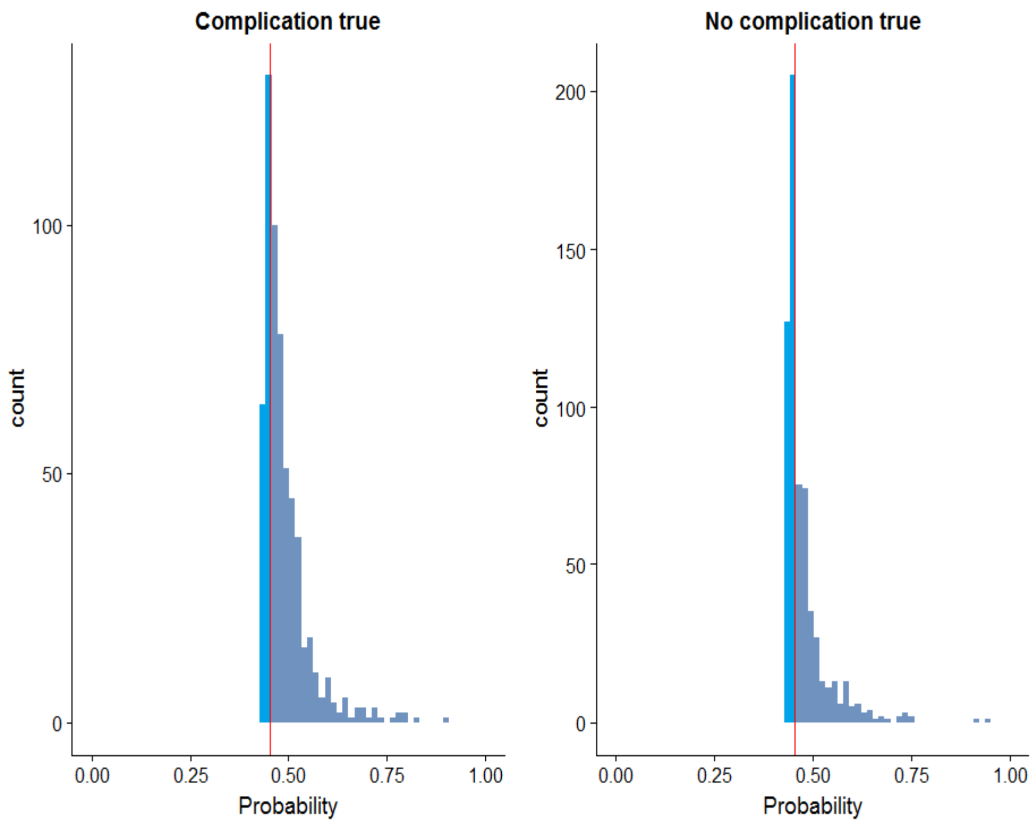

Figure 12: Histogram of predicted probabilities for a patient having postoperative complications, based on test data, if having a postoperative complication is true on the left, and if having no complications is true. The red line indicates the threshold of 0.453, which means that patients with the predicted probability higher than threshold have complications according to the model.

Figure 12 shows the predicted probabilities of patients having postoperative complications. The figure on the left shows that most patients who truly have a postoperative complication have the predicted probability higher than the threshold of 0.453, meaning that the model is good at identifying patients with complications, which also reflects the considerably high sensitivity. However, according to the figure on the right, many patients who actually have no complications have the predicted probability higher than the threshold, meaning that the model is not very good at identifying patients without postoperative complications. This is also shown by specificity in Figure 11.

6.4. Summary

In this chapter, the postoperative complications amongst patients undergoing CABG, valve and combined CABG and valve surgeries were discussed. The prevalence of postoperative complications was considerably high: 48.65%, including 78 different complications. The common complications were atrial fibrillation, need for inotropes, need for CPAP, return to theatre and pulmonary infection.

6.4.1. Highly significant variables associated with postoperative complications

The adjusted odds ratios were calculated by combining all significant variables for predicting postoperative complications. The highly significant variables associated with postoperative complications were found out to be the following:

- Patient being 75 or older (OR=2.22, 95% CI 1.79-2.76)
- Having a poor LV function (OR=1.85, 95% CI 1.18-2.94)
- Being at a critical pre-operative state (OR=2.30, 95% CI 1.10-5.18)
- Having a combined valve and CABG procedure (OR=1.52, 95% CI 1.22-1.88)

Logistic EuroSCORE was found to be associated with postoperative complications, with each increasing unit of logistic EuroSCORE the patient is 1.05 (95% CI 1.04-1.06) times more likely to have postoperative complications. Also, according to the preoperatively calculated logistic EuroSCORE being 20 or higher, the high risk patients were 2.15 (95% CI 1.40-3.37) times more likely to have postoperative complications.

6.4.2. Performance of the models

The local model predicting postoperative complications includes eight variables: age, previous MI, NYHA grade, rhythm, LV function, renal impairment, critical preoperative state and the type of procedure.

The local model and the logistic EuroSCORE model predicting postoperative complications have both moderate predictive ability, with the AUC=0.636 and

AUC=0.613. The sensitivity (65.7%) and specificity (54.6%) of the local model indicate that the model is not particularly good at identifying patients with complications and without complications. This is also shown by predicted probabilities, where number of patients with the predicted probabilities lower and higher than the threshold is almost equal for cases if having a complication is true and if having no complication is true.

The sensitivity (74.3%) is considerably higher for the logistic EuroSCORE model than for the local model, meaning that the logistic EuroSCORE is better at identifying patients with postoperative complications. However, the sensitivity (46.5%) is lower than the sensitivity of the local model.

Overall, based on the AUC of both models, the local model has a better predicting performance. The not particularly good performance could be connected to a very wide range of different postoperative complications, varying in severity of illness. This might also be the reason why some questionable variables such as sinus rhythm and unknown renal function are included as risk factors in the model.

Chapter Seven: Predicting severe postoperative complications

Of all admissions, 4.95% of the patients had severe postoperative complications. Based on the classification of the severity of complications, 19 different complications were considered to be severe. The most prevalent severe complications were acute renal failure (1.59%, 95% CI 1.24-2.05%), deep sternal wound infection (1.27%, 95% CI 0.96-1.68%) and septicaemia (1.11%, 95% CI 0.82-1.50%). The full list of severe complications recorded and the prevalence of each can be found from Appendix C.

7.1. Variables associated with severe postoperative complications

Based on chi-square test of independence, the patient characteristics, cardiac pre-operative variables, non-cardiac pre-operative variables, and surgical variables found in Table 23, 24, 25 and 26 were analysed. For all these variables unadjusted and adjusted odds ratios were obtained in order to see which variables affect patients having severe postoperative complications. The adjusted odds ratios were obtained by all variables with significant unadjusted odds ratios.

From Table 23 it can be seen that higher age gives the patient a higher likelihood of having severe postoperative complications. Although based on unadjusted odds ratios, each age group is a significant risk factor of severe postoperative complications on their own, the adjusted odds ratios show that the highest age group is the only significant age group when combined with other variables. Patients aged 75 to 99 are 2.09 (95% CI 1.25-3.55) times more likely to have severe postoperative complications than patients aged 60 and under. Figure 13 shows that for patients older than 60 the odds ratio of having severe postoperative complications increases while the odds ratios for having severe complications for patients younger than 60 are uncertain due to wide 95% confidence interval due to small sample size.

Based on adjusted odds ratios, female patients are 1.49 (95% CI 1.06-2.10) times more likely to have severe complications than male patients. If the patient has diabetes, they are 1.44 (95% CI 1.02-2.02) times more likely to have severe complications than patients who do not have diabetes.

	Severe complication	UNADJUSTED OR (95% CI)	ADJUSTED OR (95% CI)	P-value
Age: 16 to 60	3.1%	1.00	1.00	
Age: 61 to 67	4.7%	1.55 (0.95-2.54)	1.63 (0.98-2.75)	0.0638
Age: 68 to 74	4.9%	1.61 (1.02-2.60)	1.49 (0.90-2.52)	0.1289
Age: 75 to 99	7.3%	2.51 (1.63-3.94)	2.09 (1.25-3.55)	0.0056
Sex: Male	4.2%	1.00	1.00	
Sex: Female	7.2%	1.77 (1.30-2.40)	1.49 (1.06-2.10)	0.0220
Diabetes: No	4.4%	1.00	1.00	
Diabetes: Yes	6.6%	1.55 (1.13-2.11)	1.44 (1.02-2.02)	0.0364

Table 23: Unadjusted and adjusted odds ratios for patient characteristics predicting severe postoperative complications with 95% confidence intervals and P values

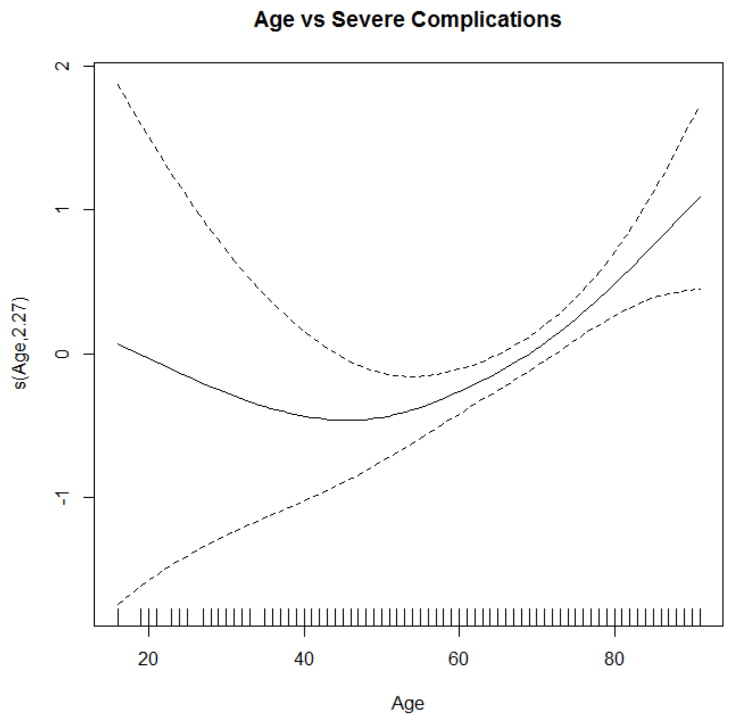

Figure 13: Age vs severe complications, using GAM, where the solid line is the odds ratios for having severe complications for each age group, and is bounded by 95% CI

Based on Table 24, congestive cardiac failure is a highly significant variable associated with severe postoperative complications on its own, however based on adjusted odds ratios only having congestive cardiac failure in the past, when combined with other variables, is no longer significant (p=0.2491). Patients who are having congestive cardiac failure at admission are 3.70 (95% CI 1.76-7.56) times more likely to have severe complications than patients who have not had congestive cardiac failure.

If the patient has had myocardial infarction, they are 1.64 (95% CI 1.13-2.38) times more likely to have severe complications than patients who have never had myocardial infarction. If having active endocarditis, the patient is 3.64 (95% CI 0.99-11.40) times more likely to have severe postoperative complications than without active endocarditis. Also, with a hypertension history, a patient is 1.56 (95% CI 1.05-2.39) times more likely to have severe complications than patient who has not had hypertension.

The NYHA grade is a highly significant risk factor for severe postoperative complications on its own, however when combined with other variables, it becomes insignificant. Based on unadjusted odds ratios, patients with NYHA Grade IV are highly likely (OR=4.57, 95% CI 2.17-9.31) to have severe postoperative complications.

The rhythm of the heart before surgery is significantly associated with severe postoperative complications based on unadjusted odds ratios, however it is no longer significant when combined with other variables. Based on unadjusted odds ratio, a patient with an abnormal rhythm is 2.04 (95% CI 1.31-3.07) times more likely to have severe postoperative complications than patients with a sinus rhythm.

With a poor LV function, a patient is 2.26 (95% CI 1.08-4.43) times more likely to have severe complications than a patient with a good LV function.

Having extracardiac arteriopathy is a significant risk factor for severe postoperative complications as a variable on its own. Based on unadjusted odds ratio, patients with extracardiac arteriopathy are 1.52 (95% CI 1.02-2.20) times more likely to have severe complications. However, when combined with other variables, the effect of this diminishes (p=0.3143).

		UNADJUSTED	ADJUSTED	
	Severe complication	OR (95% CI)	OR (95% CI)	P-value
Congestive Cardiac Failure: Never	4.2%	1.00	1.00	
Congestive Cardiac Failure: Now	25.6%	7.81 (4.54-12.98)	3.70 (1.76-7.56)	0.0004
Congestive Cardiac Failure: Past	9.2%	2.29 (1.35-3.69)	1.39 (0.77-2.37)	0.2491
Previous MI: No	4.4%	1.00	1.00	
Previous MI: Yes	5.7%	1.38 (1.02-1.86)	1.64 (1.13-2.38)	0.0098
Active Endocarditis: No	23.5%	1.00	1.00	
Active Endocarditis: Yes	29.6%	6.91 (2.68-15.84)	3.64 (0.99-11.40)	0.0360
Hypertension History: No	3.4%	1.00	1.00	
Hypertension History: Yes	5.5%	1.66 (1.15-2.46)	1.56 (1.05-2.39)	0.0327
NYHA Grade: I - No limitation of physical activity	3.3%	1.00	1.00	
NYHA Grade: II - Slight limitation of ordinary physical activity	4.2%	1.28 (0.81-2.12)	1.11 (0.69-1.88)	0.6740
NYHA Grade: III - Marked limitation of ordinary physical activity	6.8%	2.17 (1.35-3.61)	1.17 (0.70-2.04)	0.5592
NYHA Grade: IV - Symptoms at rest or minimal activity	13.4%	4.57 (2.17-9.31)	1.27 (0.50-3.04)	0.5952
Rhythm: Sinus rhythm	4.6%	1.00	1.00	
Rhythm: Abnormal rhythm	8.9%	2.04 (1.31-3.07)	1.22 (0.74-1.95)	0.4198
Rhythm: Unknown	5.1%	1.12 (0.62-1.87)	0.92 (0.50-1.59)	0.7697
LV Function: Good (LVEF >50%)	4.4%	1.00	1.00	
LV Function: Moderate (LVEF 31-50%)	6.2%	1.46 (0.99-2.10)	1.11 (0.72-1.68)	0.6134
LV Function: Poor (LVEF <30%)	15.7%	4.08 (2.25-6.98)	2.26 (1.08-4.43)	0.0229
Extracardiac Arteriopathy: No	4.7%	1.00	1.00	
Extracardiac Arteriopathy: Yes	6.9%	1.52 (1.02-2.20)	1.24 (0.81-1.86)	0.3143

Table 24: Unadjusted and adjusted odds ratios for cardiac pre-operative variables predicting severe postoperative complications with 95% CIs and P values

As it can be seen from Table 25, none of the non-cardiac pre-operative variables are significant based on adjusted odds ratios, however they were significantly associated with severe postoperative complications on their own.

Based on unadjusted odds ratio, having a pulmonary disease, a patient is 1.51 (95% CI 1.06-2.11) times more likely to have severe postoperative complications than patients without a pulmonary disease. Patients with a serum creatinine 200µmol/L or higher are highly likely (OR=3.61, 95% CI 1.21-8.73) to have severe complications after surgery, compared to patients with a normal creatinine level. Patients with a severely impaired renal function are 2.49 (95% CI 1.28-4.60) times, with moderate renal function are 1.79 (95% CI 1.14-2.84) times, and patients with an unknown renal function are 1.86 (95% CI 1.27-2.78) times more likely to have severe postoperative complications than patients with a normal renal function.

		UNADJUSTED	ADJUSTED	
	Severe complication	**OR (95% CI)**	**OR (95% CI)**	**P-value**
Pulmonary Disease: No	4.6%	1.00	1.00	
Pulmonary Disease: Yes	6.7%	1.51 (1.06-2.11)	1.26 (0.86-1.82)	0.2191
Creatinine: Under 200	4.9%	1.00	1.00	
Creatinine: 200 or over	15.6%	3.61 (1.21-8.73)	1.85 (0.51-5.33)	0.2950
Renal Impairment: Normal renal function	3.2%	1.00	1.00	
Renal Impairment: Moderate impaired renal function	5.5%	1.79 (1.14-2.84)	1.27 (0.78-2.07)	0.3409
Renal Impairment: Severely impaired renal function	7.5%	2.49 (1.28-4.60)	1.29 (0.61-2.60)	0.4851
Renal Impairment: Unknown	5.7%	1.86 (1.27-2.78)	1.43 (0.94-2.19)	0.0971

Table 25: Unadjusted and adjusted odds ratios for non-cardiac pre-operative variables predicting severe postoperative complications with 95% CIs and P values

Table 26 shows that surgical priority, critical pre-operative state and previous PCI are significantly associated with severe postoperative complications on their own, however are no longer significant when combined with other variables. Based on unadjusted odds ratios, patients with an emergency surgery are highly likely (OR=4.68, 95% CI 1.54-11.67) to have severe complications, compared to patients undergoing an elective surgery. Also, patients who are in a critical pre-operative state are 3.93 (95% CI 1.58-8.46) times more likely to have severe complications than patients who are not in a critical state. Patients who have had a PCI before are 1.68 (95% CI 1.14-2.42) times more likely to have severe complications than patients who have not had it.

Based on adjusted odds ratios, a patient having a combined valve and CABG surgery is 1.63 (95% CI 1.04-2.53) times more likely to have severe postoperative complications than a patients who undergoes CABG only. If a patient has had a previous cardiac surgery, they are 3.36 (95% CI 1.74-6.19) times more likely to have severe postoperative complications than patients who have not had a cardiac surgery before.

		UNADJUSTED	ADJUSTED	
	Severe complication	OR (95% CI)	OR (95% CI)	P-value
Priority: Elective	4.8%	1.00	1.00	
Priority: Emergency	19.2%	4.68 (1.54-11.67)	2.02 (0.45-6.81)	0.3020
Priority: Prioritised	3.2%	0.66 (0.31-1.24)	0.66 (0.30-1.29)	0.2611
Priority: Urgent	5.9%	1.23 (0.81-1.80)	0.71 (0.42-1.15)	0.1773
Critical Pre. Op. State: No	4.8%	1.00	1.00	
Critical Pre. Op. State: Yes	16.7%	3.93 (1.58-8.46)	1.32 (0.38-3.87)	0.6362
Procedure: CABG	3.7%	1.00	1.00	
Procedure: Valve	6.3%	1.75 (1.24-2.45)	1.31 (0.83-2.05)	0.2422
Procedure: Valve and CABG	7.8%	2.19 (1.47-3.22)	1.63 (1.04-2.53)	0.0304
Previous operations: No prev. cardiac surgery	4.5%	1.00	1.00	
Previous operations: Cardiac surgery	21.5%	5.75 (3.34-9.49)	3.36 (1.74-6.19)	0.0002
Previous PCI: No	4.6%	1.00	1.00	
Previous PCI: Yes	7.5%	1.68 (1.14-2.42)	1.49 (0.97-2.24)	0.0613

Table 26: Unadjusted and adjusted odds ratios for surgical variables predicting severe postoperative complications with 95% CIs and P values

7.2. Local model predicting severe complications

As seen in Section 7.1, the significant variables predicting severe postoperative complications include age, sex, diabetes, congestive cardiac failure, previous MI, active endocarditis, hypertension, LV function, type of procedure and if the patient had a previous cardiac surgery.

Using the training data obtained in Section 6.2, the logistic regression model was developed, using forward selection:

$$\begin{aligned} Severe\ postoperative\ complication = \text{Yes} \sim Age + Sex + Diabetes + \\ +Previous\ MI + Active\ Endocarditis + \\ +Hypertension + \\ +LV\ Function + Previous\ Cardiac\ Surgery \end{aligned} \quad (18)$$

According to the model estimates (Table 27), female patients aged 75 or over with diabetes, poor LV function and previous cardiac surgery, hypertension, active endocarditis and previous MI are highly likely to have severe postoperative complications.

Variable	Level	Estimate	Std. Error	z value	Pr(>|z|)	OR (95% CI)
(Intercept)		-4.7091	0.3373	-13.961	<0.001	
Age	16 to 60	0				1
	61 to 67	0.5743	0.3208	1.79	0.0734	1.78 (0.95-3.38)
	68 to 74	0.4723	0.315	1.5	0.1337	1.60 (0.87-3.03)
	75 to 99	1.0369	0.2968	3.493	0.0005	2.82 (1.60-5.17)
Sex	Male	0				1
	Female	0.5155	0.2029	2.541	0.0111	1.67 (1.12-2.48)
Diabetes	No	0				1
	Yes	0.5277	0.2033	2.596	0.0094	1.70 (1.13-2.52)
LV function	Good	0				1
	Moderate	0.4372	0.2419	1.807	0.0707	1.55 (0.95-2.46)
	Poor	1.5123	0.4013	3.769	0.0002	4.54 (1.96-9.58)
Previous cardiac surgery	No	0				1
	Yes	1.6073	0.3674	4.374	<0.001	4.99 (2.33-9.93)
Hypertension	No	0				1
	Yes	0.4808	0.2501	1.922	0.0546	1.62 (1.01-2.70)
Active endocarditis	No	0				1
	Yes	2.4764	0.6053	4.091	<0.001	11.90 (3.41-37.59)
Previous MI	No	0				1
	Yes	0.4487	0.2032	2.208	0.0273	1.57 (1.05-2.33)

Table 27: Coefficients of the model with their estimates, standard errors, z values, p values and odds ratios with 95% CIs

Using the test data, in order to measure the performance of the model, the ROC curve was obtained (Figure 14). The area under the curve of ROC was 0.685 with the sensitivity of 86.9%, specificity of 46.8%, PPV of 1.5% and NPV of 92.1%. The sensitivity indicates that 86.9% of the time the model identifies patients with severe postoperative complications correctly. The specificity shows that the model identifies patients without severe postoperative complications correctly 46.8% of the time. According to the PPV, if the test is positive, the probability that the patient has a severe complication is only 1.5%. However, according to the NPV, if the test is negative, the probability that the patient does not have a severe complication is 92.1%.

However, PPV and NPV are influenced by the prevalence of disease in the population that is being tested. In our population 4.95% of the patients had severe complications, which is considerably low prevalence, and therefore the PPV is very low and NPV very high.

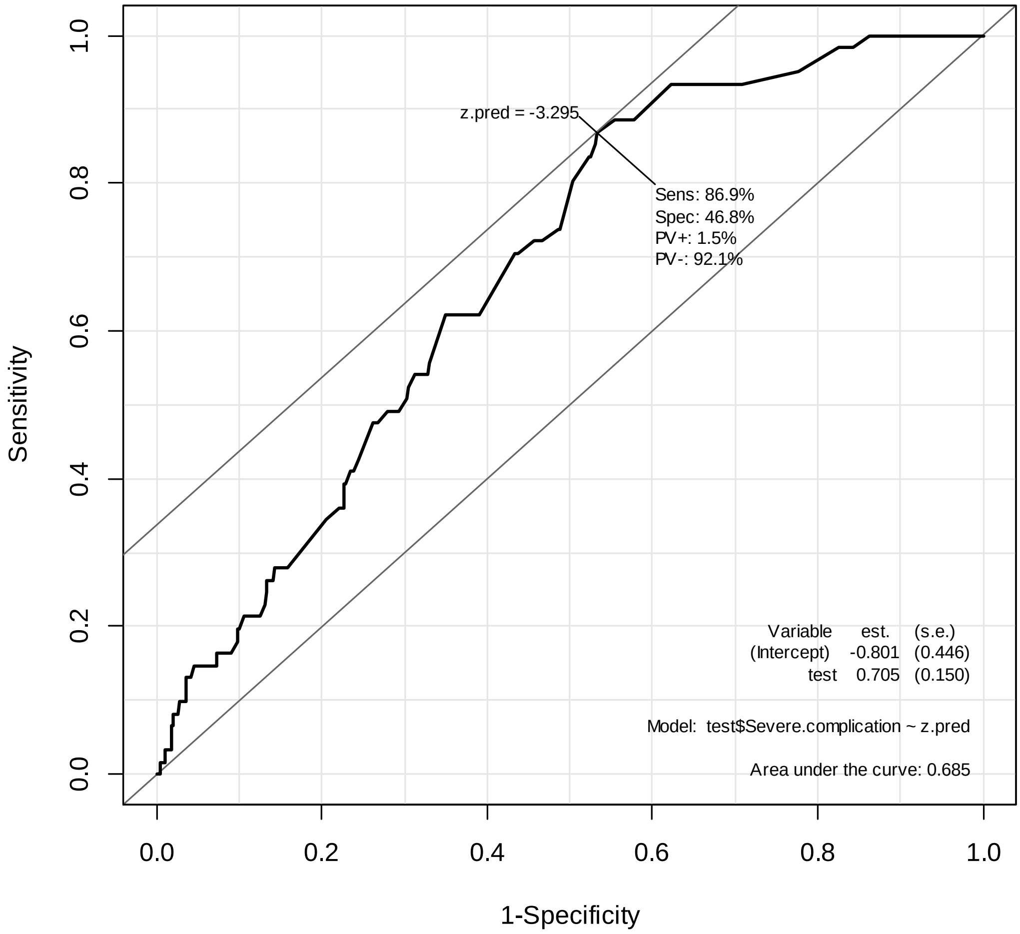

Figure 14: ROC curve of the local model predicting severe postoperative complications, based on test data

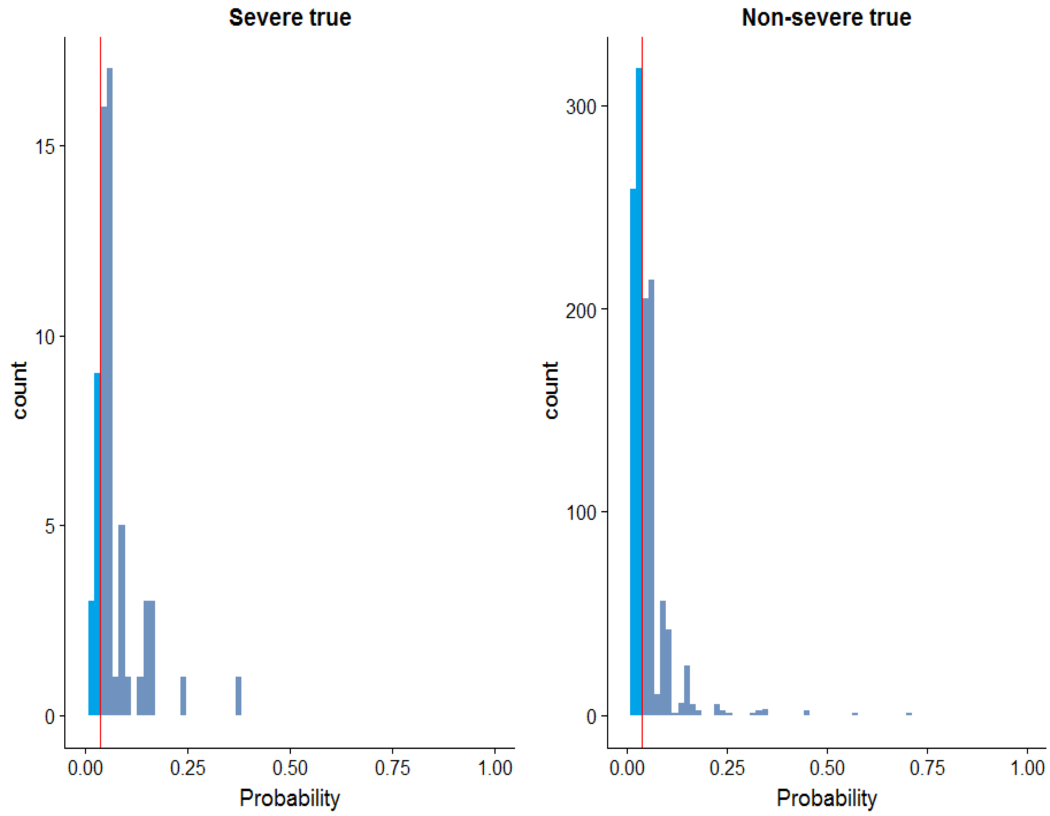

Figure 15: Predicted probabilities of patient having severe postoperative complications, based on test data, if severe complication is true on the left, and if non-severe complication is true on the right. The red line is the threshold of 0.036, meaning the predicted probability higher than that indication patients having severe complications according to the model.

Figure 15 shows that the number of patients having a severe complication is low, however most patients have the predicted probability of having severe complications over the threshold of 0.036, meaning that the model is good at identifying patients with severe complications, as also seen from sensitivity. However, the figure on the right shows that many patients have non-severe complications, but still a considerably high number of patients have the predicted probability over the threshold, meaning that the model is not good at identifying patients without severe complications. This was also seen from the low specificity from the ROC curve.

7.3. Logistic EuroSCORE predicting severe complications

Both Table 28 and 29 show that logistic EuroSCORE is a highly significantly associated with severe postoperative complications with the p <0.001.

The higher the preoperatively calculated logistic EuroSCORE, the higher is the likelihood of having a severe postoperative complication. From the Table 28 it can be seen that the patients with the logistic EuroSCORE higher than or equal to 20 are 5.75 (95% CI 3.34-9.49) times more likely to have severe postoperative complications.

Variable	Severe complication	OR (95% CI)	P-value
Logistic EuroSCORE < 20	4.43%	1.00	
Logistic EuroSCORE ≥ 20	0.54%	5.75 (3.34-9.49)	<0.001

Table 28: Odds ratios for patients with logistic EuroSCORE <20 and with logistic EuroSCORE ≥ 20 having a severe complication, with 95% CI and P value

Table 29 shows that with each increasing unit of logistic EuroSCORE, the patient is 1.06 (95% CI 1.05-1.08) times more likely to have a severe complication.

Variable	Severe complication	OR (95% CI)	P-value
Logistic EuroSCORE	4.97%	1.06 (1.05-1.08)	<0.001

Table 29: Odds ratio for logistic EuroSCORE increasing with each unit with 95% CI and P-value

The Figure 16 shows that just like when predicting postoperative complications in general, we can be more certain about the increase of likelihood of having severe postoperative complications when logistic EuroSCORE increases from 0 to 20, and not so certain about patients whose logistic EuroSCORE is 20 or more due to the small sample size for patients with a high logistic EuroSCORE.

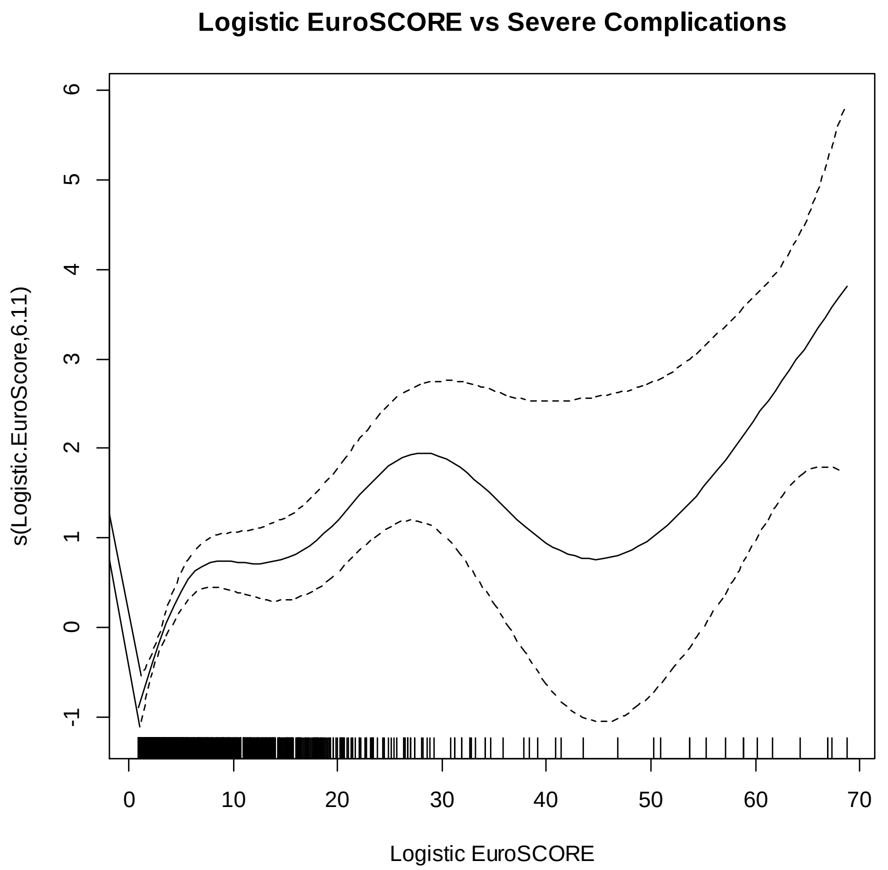

Figure 16: Logistic EuroSCORE vs severe postoperative complications, where the odds ratio is the main line and is bounded by 95% CI

For developing a prediction model predicting severe postoperative complications, training data used in Section 6.2 was used:

$$Severe\ postoperative\ complication = Yes \sim Logistic\ EuroSCORE \tag{19}$$

Coefficients	Estimate	Std. Error	z value	Pr(>|z|)	OR (95% CI)
(Intercept)	-3.3287				
Logistic EuroSCORE	0.0564	0.0084	6.706	<0.001	1.06 (1.04-1.08)

Table 30: Estimated, standard error, z-value, p-value and odds ratios with 95% CI for the model

As it can be seen from Table 30, logistic EuroSCORE is a highly significant variable for severe postoperative complications on a 95% significance level. According to the model estimate, with every increasing unit of logistic EuroSCORE, the log odds of having severe postoperative complications increase 0.0564 times. According to standard error, on average the estimate would vary 0.0084 times if the model would be run identically using different data.

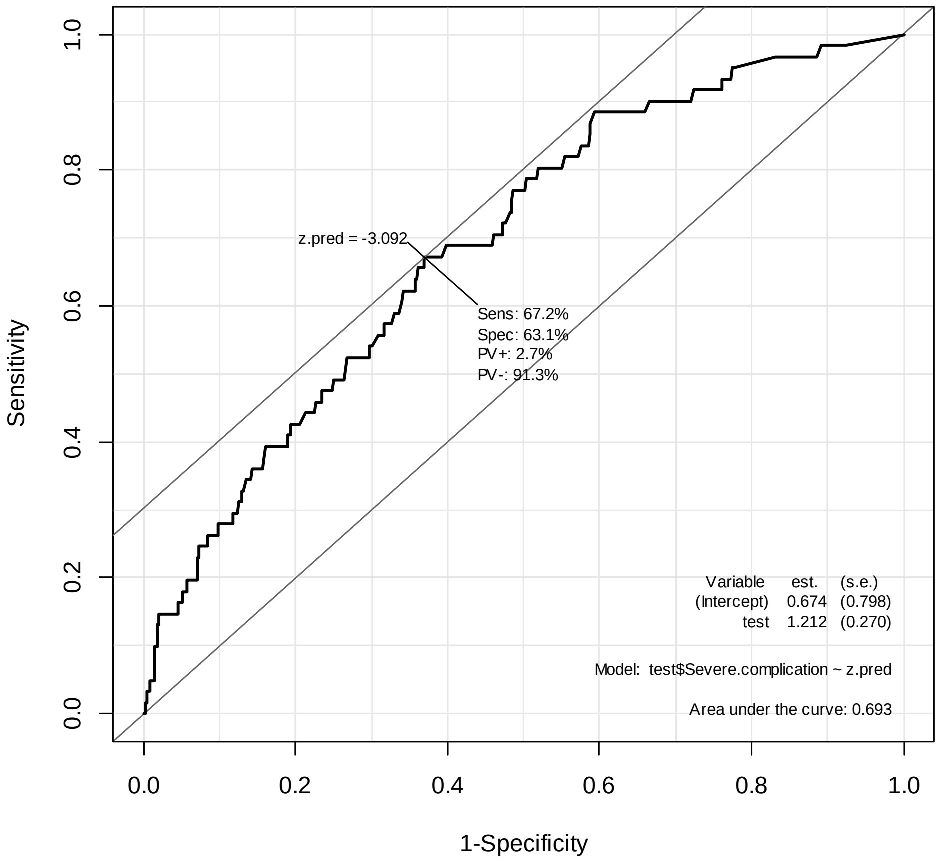

Figure 17: ROC curve for logistic EuroSCORE predicting severe postoperative complications, using the test data

Using the test data, the ROC curve was created (Figure 17) in order to measure the performance of the model. The area under the curve was 0.693 with the sensitivity of 67.2%, specificity of 63.1%, PPV of 2.7% and NPV of 91.3%. This means that the model identifies patients with severe complications correctly 67.2% of the time, and patients without severe complications 63.1% of the time. The probability of having a severe complication when the test is positive is very low: 2.7%. However, when the test is negative, the probability of patients not having a severe complication is 91.3%, which is extremely high, which is due to considerably low prevalence of severe postoperative complications.

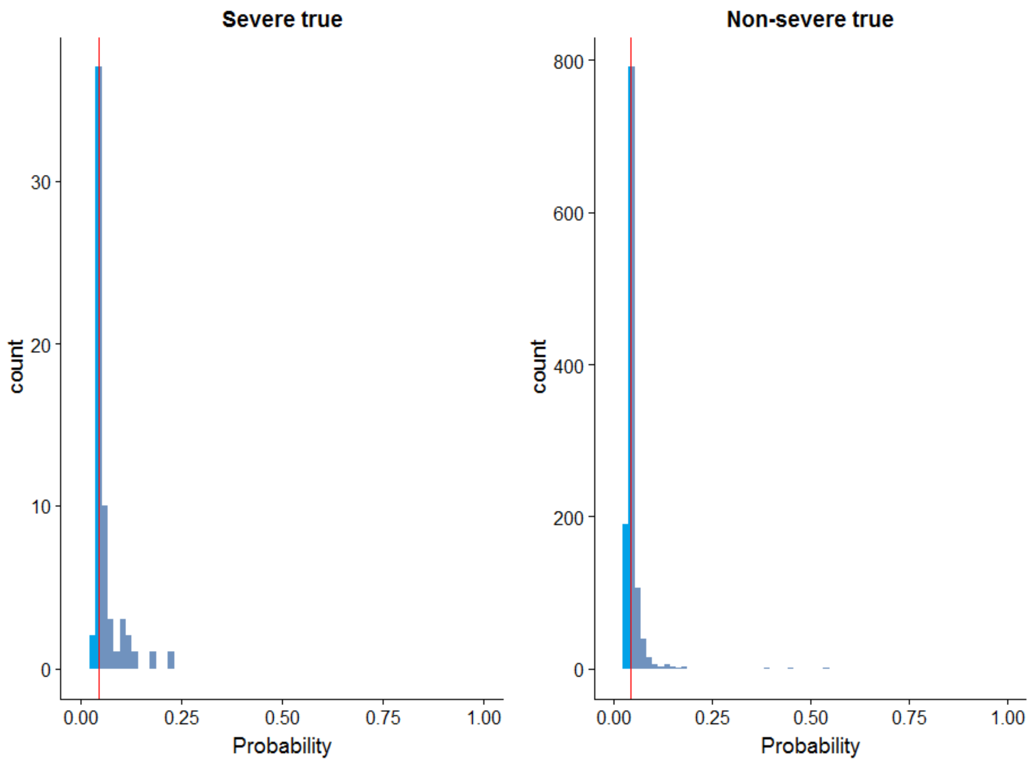

Figure 18: Predicted probabilities of patient having severe complications, based on test data, if having a severe postoperative complication is true on the left, and if non-severe complication is true on the right. The red line indicates the threshold of 0.043, meaning that predicted probability higher than the threshold indicates patients with severe complications according to the model.

The Figure 18 shows the predicted probabilities of patients having severe complications. The figure on the left shows that not many patients actually have severe complications, however most of the predicted probabilities are higher than the threshold of 0.043, meaning that the model is good at identifying patients with severe complications. This is also reflected by the sensitivity of the model. The figure on the right shows that many patients have non-severe or no complications, with some patients having the predicted probability higher than the threshold. According to that, the model has a moderate ability at identifying patients without severe complications, which is also shown by specificity in Figure 17.

7.4. Summary

This chapter was focused on finding risk factors and developing a prediction model for severe postoperative complications. The prevalence of severe complications was

4.95%, the most common severe complications being acute renal failure, deep sternal wound infection and septicaemia.

7.4.1. Highly significant variables associated with severe complications

The variables that are highly significantly associated with severe postoperative complications were found to be the following:

- Patient being 75 or older (OR=2.09, 95% CI 1.25-3.55)
- Patient having a congestive cardiac failure at admission (OR=3.70, 95% CI 1.76-7.56)
- Having active endocarditis (OR=3.64, 95% CI 0.99-11.40)
- Having a poor LV function (OR=2.26, 95% CI 1.08-4.43)
- Having had a cardiac surgery in the past (OR=3.36, 95% CI 1.74-6.19).

7.4.2. Performance of the models

The significant variables included in the prediction model are age, sex, diabetes, LV function, previous cardiac surgery, hypertension, active endocarditis and previous MI. The performance of the local model and the logistic EuroSCORE model appears to be similar with the AUC=0.685 and AUC=0.693, respectively. However, the differences come in with the sensitivity and specificity of the models. The local model has considerably higher sensitivity than the logistic EuroSCORE (86.9% vs 67.2%) which shows that the local model is better at identifying patients with severe complications. However, logistic EuroSCORE has a higher specificity than the local model (63.1% vs 46.8%). Although, logistic EuroSCORE appears to be better at identifying patients without severe complications, both models do not have a particularly high specificity. The performance of the model is also shown by predicted probabilities where for the local model, most patients who truly have a severe complications, have the probability higher than the threshold. The predicted probabilities for both models do not show a clear result at identifying patients without severe complications, which is also explained by specificity of both models.

Chapter Eight: Predicting the level of postoperative complication

Of all treated patients, 51.35% had no complications, 7.05% had mild complications, 36.65% had moderate complications and 4.95% had severe complications. Although the prediction model predicting severe postoperative complications has been developed, we would like to find out if it would be possible to develop a prediction model predicting the level of postoperative complication based on our data. For this ordinal logistic regression was used.

Overall, 17 different mild complications, 42 different moderate and 19 different severe complications were identified. The most common mild complications were the use of inotropes (13.73%) and requirement of continuous positive airway pressure (CPAP) (8.97%). The most common moderate complications were atrial fibrillation (28.41%) and need to return to the theatre (5.19%). As mentioned in Chapter Seven, the most common severe complications were acute renal failure (1.59%) and deep sternal wound infection (1.27%). The occurrence of all complications can be found from Appendix C.

8.1. Variables associated with a higher level of postoperative complication

The adjusted odds ratios were obtained by combining all significant variables associated with a higher level of postoperative complication. Only significant variables based on adjusted odds ratios were included in Table 31, which are age, smoking status, renal function, procedure, LV function, NYHA grade, rhythm, previous cardiac surgery, previous MI, LMS status and congestive cardiac failure.

The risk factors associated with a higher complication level are age groups 61 to 67, 68 to 74 and 75 to 99, having an unknown smoking status, having an unknown renal function, undergoing valve surgery or combined valve and CABG surgery, having poor LV function, having NYHA grade IV, having a previous MI, previous cardiac surgery, having an unknown LMS status and having had congestive cardiac failure in the past.

Variable	No	Mild	Moderate	Severe	OR (95% CI)	P-value
Age: 16 to 60	63.5%	7.7%	25.7%	3.1%	1.00	
Age 61 to 67	51.0%	8.5%	35.8%	4.7%	1.70 (1.40-2.05)	<0.001
Age: 68 to 74	47.9%	6.2%	41.0%	4.9%	1.93 (1.59-2.33)	<0.001
Age: 75 to 99	42.4%	6.1%	44.3%	7.2%	2.31 (1.88-2.85)	<0.001
Smoking Status: No	53.5%	7.3%	34.8%	4.5%	1.00	
Smoking Status: Current smoker	55.2%	9.2%	31.6%	3.9%	1.12 (0.88-1.43)	0.3424
Smoking Status: Ex-smoker	51.8%	5.9%	36.5%	5.8%	1.16 (0.97-1.39)	0.1141
Smoking Status: Unknown	48.4%	7.2%	39.6%	4.8%	1.24 (1.05-1.48)	0.0135
Renal Impairment: Normal	57.9%	8.4%	30.5%	3.2%	1.00	
Renal Impairment: Moderate	50.3%	6.5%	37.7%	5.5%	1.09 (0.90-1.32)	0.3598
Renal Impairment: Severe	43.5%	2.7%	46.2%	7.5%	1.31 (0.94-1.83)	0.1048
Renal Impairment: Unknown	48.0%	6.9%	39.5%	5.7%	1.33 (1.14-1.56)	0.0004
Procedure: CABG	55.1%	7.5%	33.8%	3.7%	1.00	
Procedure: Valve	48.7%	6.6%	38.4%	6.3%	1.35 (1.12-1.62)	0.0013
Procedure: CABG and Valve	40.5%	6.0%	45.6%	7.8%	1.54 (1.26-1.89)	<0.001
LV Function: Good (LVEF > 50%)	52.1%	6.6%	37.0%	4.3%	1.00	
LV Function: Moderate (LVEF 31-50%)	50.4%	9.1%	34.2%	6.2%	0.97 (0.81-1.16)	0.7497
LV Function: Poor (LVEF < 30%)	34.3%	8.8%	41.2%	15.7%	1.95 (1.29-2.97)	0.0016
NYHA Grade: I	57.1%	6.7%	32.9%	3.3%	1.00	
NYHA Grade: II	52.4%	7.2%	36.3%	4.2%	1.10 (0.92-1.31)	0.3046
NYHA Grade: III	47.3%	6.6%	39.3%	6.7%	1.14 (0.93-1.40)	0.2142
NYHA Grade: IV	33.0%	11.3%	42.3%	13.4%	1.67 (1.08-2.61)	0.0224
Rhythm: Sinus	50.3%	6.9%	38.3%	4.6%	1.00	
Rhythm: Abnormal	58.7%	10.8%	21.9%	8.6%	0.49 (0.38-0.63)	<0.001
Rhythm: Unknown	54.2%	5.1%	35.6%	5.1%	0.82 (0.64-1.06)	0.1305
Previous Cardiac Surgery: No	51.4%	7.2%	36.8%	4.5%	1.00	
Previous Cardiac Surgery: Yes	48.4%	1.1%	29.0%	21.5%	1.55 (0.99-2.42)	0.0538
Previous MI: No	52.8%	6.1%	36.7%	4.4%	1.00	
Previous MI: Yes	48.9%	8.6%	36.6%	5.9%	1.30 (1.11-1.51)	0.0009
LMS: No LMS disease	48.3%	7.5%	39.0%	5.1%	1.00	
LMS: > 50% diameter stenosis	49.2%	5.5%	40.5%	4.9%	1.09 (0.88-1.35)	0.4342
LMS: Unknown	54.3%	7.1%	33.8%	4.8%	0.84 (0.73-0.97)	0.0180
Congestive Cardiac Failure: No	52.3%	7.1%	36.4%	4.2%	1.00	
Congestive Cardiac Failure: Now	42.7%	6.1%	25.6%	25.6%	1.33 (0.80-2.22)	0.2717
Congestive Cardiac Failure: Past	39.6%	6.8%	44.4%	9.2%	1.34 (1.01-1.78)	0.0429
No|Mild						<0.001
Mild|Moderate						<0.001
Moderate|Severe						<0.001

Table 31: Variables with significant adjusted odds ratios associated with a higher complication level, with 95% CIs and p-values

Age variable is associated with a higher complication level with a high significance (P<0.001). The boxplot in Figure 19 shows the change of complication level with a higher age, also indicating that more patients have either no complications or moderate complications, and less mild complications or severe complications. Therefore, Figure 19 also shows that based on the data, it is difficult to see the difference between patients with no and mild complications, and patients with moderate and severe complications.

The rectangles in the box plot (Figure 19) represent the second and third quartiles, with the vertical line indicating the median value. The lower and upper quartiles are shown as the horizontal lines either side of the rectangle.

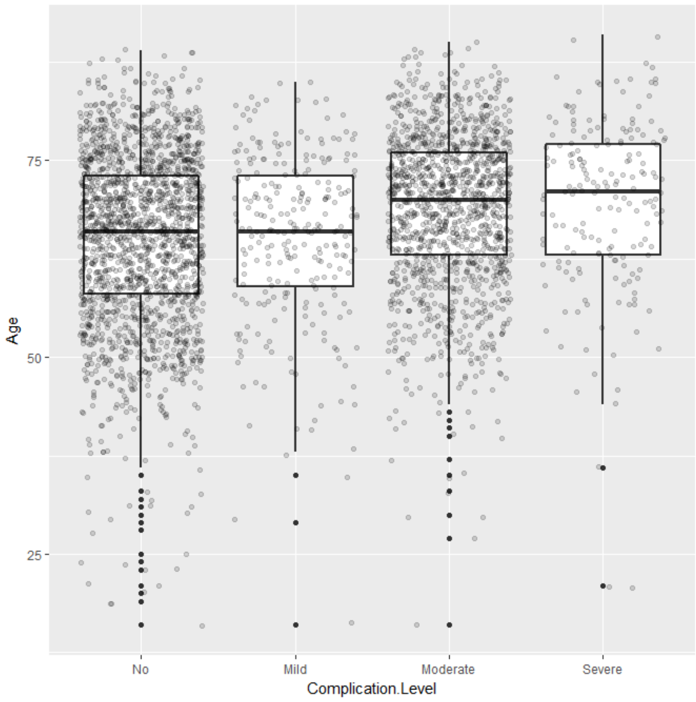

Figure 19: Box plot of patients' age and the level of postoperative complication, with the grey dots being the patients

Rhythm	No complication	Mild complication	Moderate complication	Severe complication
Abnormal rhythm (%)	185 (58.7)	34 (10.8)	69 (21.9)	27 (8.6)
Sinus rhythm (%)	1555 (50.3)	212 (6.9)	1182 (38.3)	141 (4.6)
Unknown (%)	160 (54.2)	15 (5.1)	105 (35.6)	15 (5.1)

Table 32: Patients with different levels of postoperative complications, based on the pre-operative rhythm of the heart

Similarly to Section 6.1, it is surprising that patients with abnormal rhythm before surgery are less likely to have a higher level of complication after surgery (OR=0.49, 95% CI 0.38-0.63). Table 33 shows that the majority of patients with sinus rhythm do not have any postoperative complications, however a considerably large number (38.3%) have moderate complications. As the rhythm variable only includes the information directly before surgery there is no information in our data if some of the patients with sinus rhythm have had arrhythmia problems in the past, which could be the reason for high number of moderate complications for patients with sinus rhythm.

Also, as mentioned in the beginning of Chapter Eight, the most common moderate complication was atrial fibrillation, which could be connected to the previous arrhythmia problems. According to chi squared test of independence, rhythm is significant variable connected to atrial fibrillation with the p-value of <0.001. As shown in Table 32, patients with sinus rhythm have the highest prevalence of having postoperative atrial fibrillation.

Rhythm	Postoperative Atrial fibrillation	Percentage (95% CI)
Sinus rhythm	949	30.7 (29.1-32.4)
Abnormal rhythm	21	6.7 (4.4-1.0)
Unknown rhythm	81	27.5 (22.7-32.8)

Table 33: Patients with postoperative atrial fibrillation based on the preoperative rhythm of the heart

8.2. A local model predicting the level of postoperative complications

Based on adjusted odds ratios, the significant variables associated with the higher level of postoperative complications are age, smoking status, previous MI, NYHA grade, rhythm, LV function, LMS, renal function, surgical priority and procedure.

Using the training data (2479 admissions), obtained in Section 6.2, the prediction model was developed, using ordinal logistic regression:

$$\begin{gathered} Complication\ Level \sim Age + Previous\ MI + NYHA\ Grade + \\ + Rhythm + LV\ Function + \\ + Renal\ Function + Procedure \end{gathered} \tag{20}$$

According to the model estimates, patients with higher age, with unknown renal function, with procedure other than CABG, poor LV function, with NYHA grade IV and previous MI are more likely to have a higher level of postoperative complication. Also, as explained in Section 6.1, patients with abnormal rhythm are less likely to have a higher complication level than patients with sinus rhythm.

Coefficients		Estimate	Std. Error	Z value	P value	OR (95% CI)
Age	16 to 60	0				1
	61 to 67	0.5242	0.1169	4.4832	<0.001	1.69 (1.34-2.13)
	68 to 74	0.6076	0.1144	5.3133	<0.001	1.84 (1.47-2.30)
	75 to 99	0.7925	0.1245	6.3637	<0.001	2.21 (1.73-2.82)
Renal Impairment	Normal function	0				1
	Moderate function	0.0931	0.1180	0.7891	0.4301	1.10 (0.87-1.38)
	Severely impaired	0.3373	0.1883	1.7918	0.0732	1.40 (0.97-2.03)
	Unknown	0.2583	0.0956	2.7013	0.0069	1.29 (1.07-1.56)
Procedure	CABG	0				1
	Valve	0.2228	0.1049	2.1230	0.0338	1.25 (1.02-1.53)
	Valve and CABG	0.3635	0.1246	2.9167	0.0035	1.44 (1.13-1.84)
LV Function	Good (LVEF > 50%)	0				1
	Moderate (LVEF 31-50%)	0.0656	0.1097	0.5981	0.5498	1.07 (0.86-1.32)
	Poor (LVEF < 30%)	0.9891	0.2602	3.8009	<0.001	2.69 (1.62-4.49)
NYHA Grade	I - No limitation of physical activity	0				1
	II - Slight limitation of ordinal physical activity	0.0669	0.1083	0.6172	0.5371	1.07 (0.87-1.32)
	III - Marked limitation of ordinary physical activity	0.2378	0.1216	1.9560	0.0505	1.27 (1.00-1.61)
	IV - Symptoms at rest or minimal activity	1.0545	0.2763	3.8165	<0.001	2.87 (1.67-4.95)
Rhythm	Sinus	0				1
	Abnormal	-0.6815	0.1460	-4.6674	<0.001	0.51 (0.38-0.67)
	Unknown	-0.1449	0.1516	-0.9557	0.3392	0.87 (0.64-1.16)
Previous MI	No	0				1
	Yes	0.3064	0.0918	3.3392	0.0008	1.36 (1.14-1.63)
	Intercepts					
No |Mild		0.9857	0.1359	7.2551	<0.001	
Mild |Moderate		1.2748	0.1368	9.3194	<0.001	
Moderate |Severe		4.0122	0.1658	24.1964	<0.001	

Table 34: Coefficients of the ordinal logistic regression model predicting the level of postoperative complications

In the Table 34 we can see three intercepts, which are also called cut-points. The intercepts indicate where the latent variable is cut to make the four groups observed in the data. Each data point is assigned a discrete latent variable that describes which complication level it has been assigned to.

Using the test data, also used in Section 6.2, predicted probabilities for each complication level were calculated and a confusion matrix, in order to measure the performance of the model, was obtained. Based on the predicted probabilities, the confusion matrix shows that as mild and severe complications are both considerably rare occasions, they never come up as possible results, meaning that both mild and severe complications have very low predicted probabilities.

		Predicted level			
		No	Mild	Moderate	Severe
Actual level	No	518	0	112	0
	Mild	74	0	19	0
	Moderate	292	0	145	0
	Severe	34	0	27	0

Table 35: Confusion matrix for the prediction model predicting the level of postoperative complications

Using the confusion matrix, the accuracy, sensitivity, specificity, PPV and NPV were calculated. Table 36 shows that although the model could identify patients without mild or severe complications considerably well, it does not differentiate patients between no or moderate complications.

	ACC	Sensitivity	Specificity	PPV	NPV
No	0.58	0.82	0.32	0.56	0.63
Mild	0.92	0.00	1.00	0.00	0.92
Moderate	0.63	0.33	0.80	0.48	0.68
Severe	0.95	0.00	1.00	0.00	0.95

Table 36: The accuracy, sensitivity, specificity, PPV and NPV of the prediction model, calculated based on the confusion matrix.

However, when looking at predicted probabilities, the difference between complication levels can be understood more. Based on Figure 20, the model is more likely to identify patients with no complications or with moderate complications, which is largely associated with the high prevalence for these cases. As it can be seen from Figure 20, the model rarely identifies patients having any other complication than no complication. When model classifies patients having no complications, then a very small number of patients are having the predicted probability over the threshold of 0.728, identifying patients having a mild complication. However, the predicted probabilities never reach the thresholds of 0.781, which means that a patient would have a moderate complication, and 0.982, which means that a patient would have a severe complication.

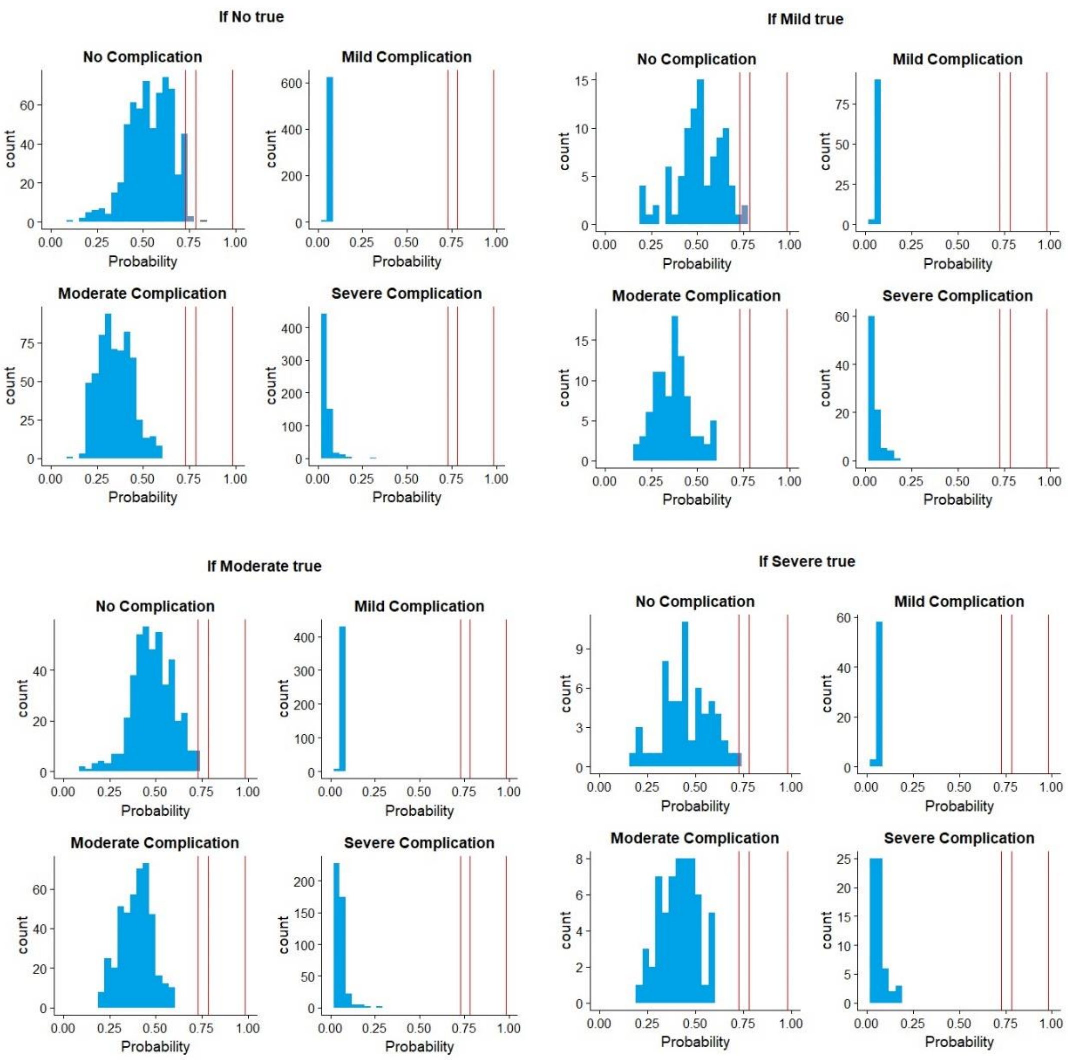

Figure 20: The predicted probabilities of patients having different complication levels, using test data, where the cut-off points from no to mild complication is 0.728, mild to moderate is 0.781, and moderate to severe is 0.982.

The reason why the model never identifies patients with severe complications might be due to the very low prevalence of severe complications. If we looked at the predicted probabilities for patients who actually did not have any complications, the picture looked similar.

If the patient has no complications, the majority of the time, the model classifies patients as not having a complication. Only a very small number of patients have the probability over the threshold for having mild complications and even a smaller amount having moderate complications.

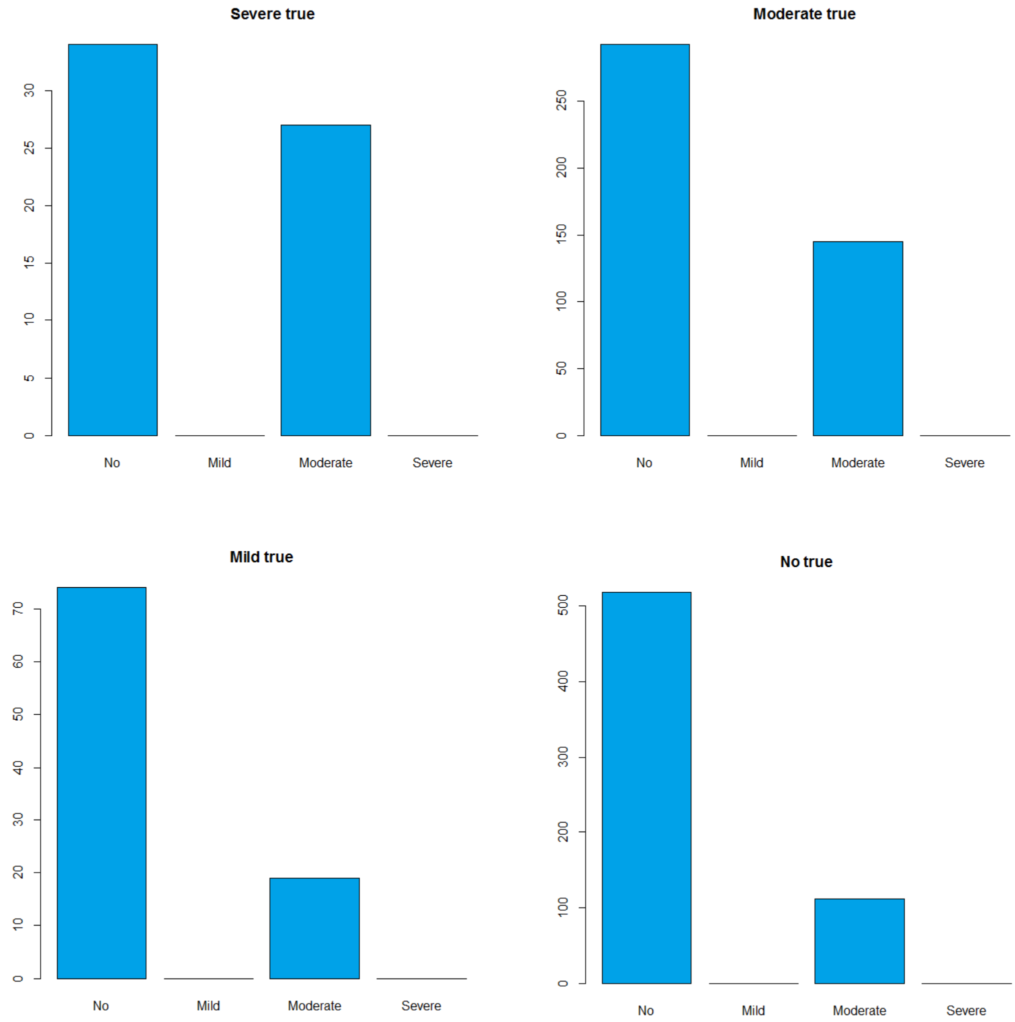

Figure 21: Predicted complication level if severe complication is true, moderate is true, mild is true and no complication is true, based on predicted probabilities

The predicted categories can be seen more clearly in Figure 21, which shows that the model only identifies patients with either no complications or with a moderate complication due to smaller prevalence of patients having a mild or severe complication. It can also be seen that patients who actually have a severe or a moderate complication are more likely to be categorised to have a moderate complication than patients with either a mild complication or a no complication.

8.3. Logistic EuroSCORE predicting the level of postoperative complications

As shown in Table 37, logistic EuroSCORE is highly significantly associated with higher level of postoperative complication ($p<0.001$), with every increasing unit of logistic EuroSCORE the patient being 1.05 (95% CI 1.04-1.06) times more likely to have a higher level of postoperative complication.

	OR (95% CI)	**P-value**
Logistic EuroSCORE	1.05 (1.04-1.06)	<0.001
No|Mild		<0.001
Mild|Moderate		<0.001
Moderate|Severe		<0.001

Table 37: Odds ratios for each increasing unit of logistic EuroSCORE having a higher complication level, with 95% CI and P-values

When comparing high risk patients with mild to moderate risk patients, Table 38 shows that patients with logistic EuroSCORE 20 or more are 2.66 (95% CI 1.77-4.03) times more likely to have a higher level of complication.

	No	**Mild**	**Moderate**	**Severe**	**P-value**	**OR (95% CI)**
Logistic EuroSCORE < 20	50.51%	6.81%	35.76%	4.41%		1
Logistic EuroSCORE ≥ 20	0.84%	0.24%	0.89%	0.54%	<0.001	2.66 (1.77-4.03)
No|Mild					0.0226	
Mild|Moderate					<0.001	
Moderate|Severe					<0.001	

Table 38: Odds ratios for patients with logistic EuroSCORE <20 and with logistic EuroSCORE ≥ 20 having a higher complication level, with 95% CI and P-values

The box plot visualised in Figure 22 shows that patients with a higher logistic EuroSCORE tend to have a higher level of complications, however the difference between no, mild and moderate complications are subtle, compared to patients with severe complications. Similarly to Section 8.1, the box plot also shows that the majority of the patients have either no complications or moderate complications.

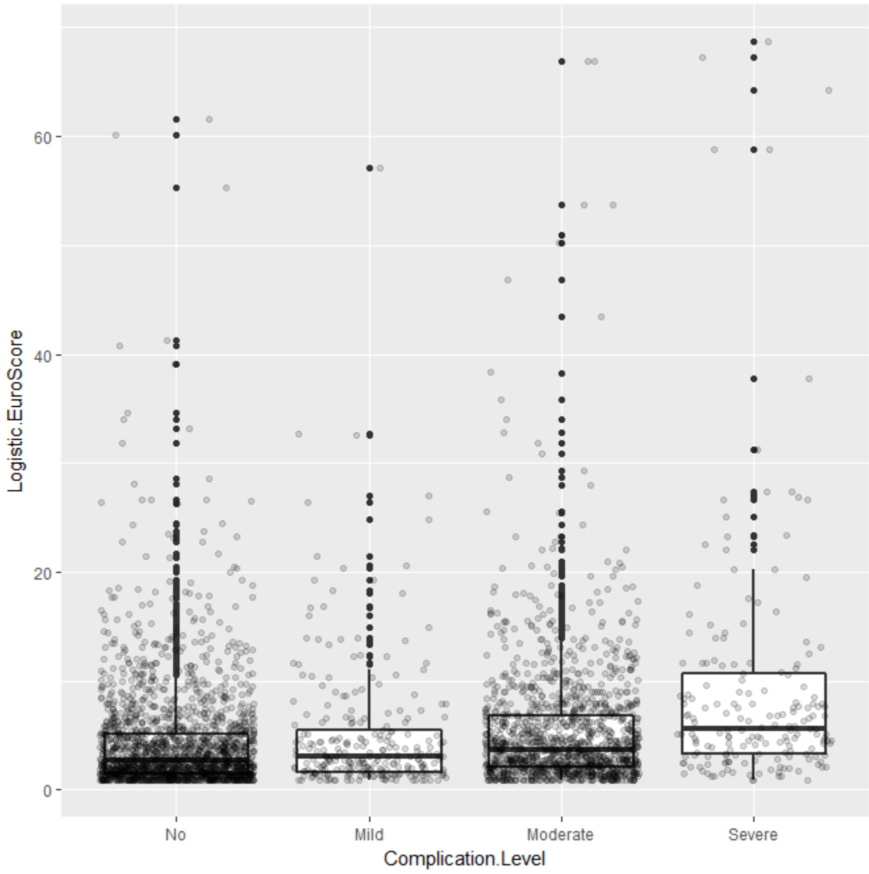

Figure 22: Box plot of preoperatively calculated logistic EuroSCORE and the level of postoperative complication

Using the training data, also used in Section 6.2, a prediction model predicting the complication level was developed. According to the model estimate in Table 39, with every increasing unit of logistic EuroSCORE the log odds of patient having a higher complication increases 0.0501 times. According to the p-value of the coefficient, logistic EuroSCORE is a highly significant variable predicting a higher level of complications with the p-value of <0.001.

Coefficients	**Estimate**	**Std. Error**	**T-value**	**P-value**	**OR (95% CI)**
Logistic EuroSCORE	0.0501	0.0062	8.0200	<0.001	1.05 (1.04-1.06)
Intercepts					
No|Mild	0.3035	0.0513	5.9185	<0.001	
Mild|Moderate	0.5822	0.0521	11.1713	<0.001	
Moderate|Severe	3.2793	0.1039	31.5749	<0.001	

Table 39: Coefficients of logistic EuroSCORE predicting the level of postoperative complications

Using the test data, in order to measure the performance of the model, predicted probabilities were calculated and a confusion matrix was created. From the confusion matrix (Table 40), it can be seen again that the model never predicts patients to have a mild or severe complication due to the small sample size of patients having mild or severe complications.

		Predicted Level			
		No	Mild	Moderate	Severe
True	No	581	0	49	0
	Mild	89	0	4	0
	Moderate	403	0	34	0
	Severe	46	0	15	0

Table 40: Confusion matrix for logistic EuroSCORE predicting the level of postoperative complication based on test data

Table 41 shows that just like with the local model, the accuracy for mild (0.92) and severe complications (0.95) is very high. Also, the NPV shows that the model identifies patients without mild or severe complications very well, however it does not identify moderate complications or if the patient does not have complications accurately.

	ACC	Sensitivity	Specificity	PPV	NPV
No	0.52	0.92	0.09	0.52	0.52
Mild	0.92	0.00	1.00	0.00	0.92
Moderate	0.61	0.08	0.91	0.33	0.64
Severe	0.95	0.00	1.00	0.00	0.95

Table 41: The accuracy, sensitivity, specificity, PPV and NPV of the model calculated from the confusion matrix

Visualising predicted probabilities helps us to understand the model more. Similarly to the local model, the logistic EuroSCORE identifies patients with no complications and moderate complications considerably well, and rarely recognises patients with mild or severe complications.

Figure 23 shows the predicted probabilities, if the patient has a severe complication. The majority of the time, the model identifies patients to have no complications, with the predicted probabilities hardly ever being higher than the threshold for having a mild complication (0.575), moderate complication (0.641) or a severe complication (0.964). As the model classifies these patients to have a moderate complication, a very small number of patient have the predicted probability high enough to have a mild complication.

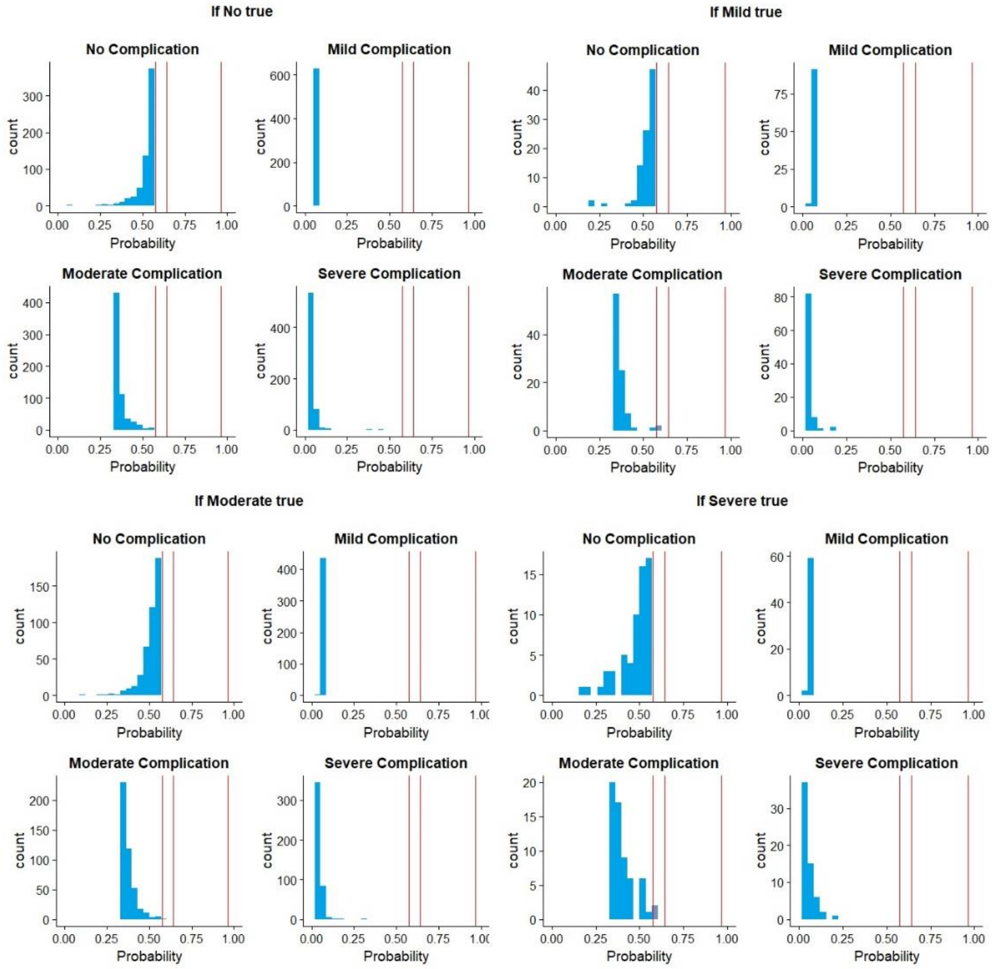

Figure 23: Histograms of predicted probabilities for each complication level, using test data. The cut-off points are for no to mild 0.575, mild to moderate 0.641, and moderate to severe 0.964

On the other hand, if not having complications is true, that the predicted probabilities are always under the threshold, meaning that the model categorises patients to have no complications.

Figure 24 shows the predicted complication levels by the model. Similarly to the local model, the majority of the time, the model categorises patients to have no complications. If the patient has a severe complication, more patients are categorised as having a moderate complication by the model, however, mild and severe complications are never identified.

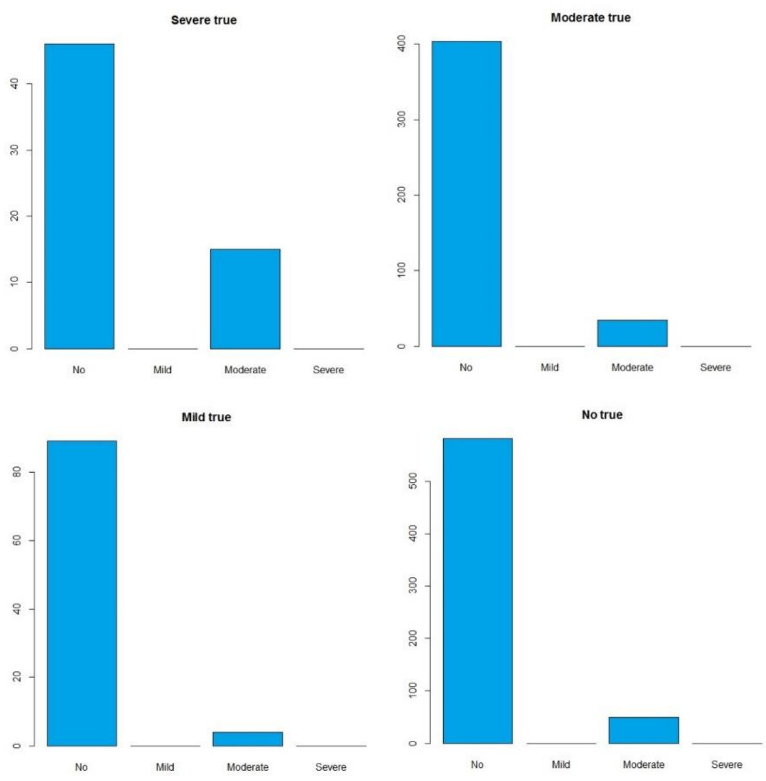

Figure 24: Predicted categories for each complication based on the model

8.4. Summary

Of all analysed patients, 7.05% had mild complications, 36.65% had moderate complications, and 4.95% had severe complications. The most common mild complications were the use of inotropes and the requirement of CPAP, common moderate complications were atrial fibrillation and the need to return to theatre, and common severe complications were acute renal failure and deep sternal wound infection.

8.4.1. Highly significant variables associated with a higher level of complication

The highest risk factors for a patient having a more severe complication were found to be the following:

- Patient being 75 or older (OR=2.31, 95% CI 1.88-2.85)
- Having a poor LV function (OR=1.95, 95% CI 1.29-2.97)
- Undergoing combined CABG and valve surgery (OR=1.54, 95% CI 1.26-1.89)
- Having the NYHA grade IV (OR=1.67, 95% CI 1.08-2.61)

8.4.2. Performance of the models

The local model includes seven variables: age, previous MI, LV function, NYHA grade, rhythm, renal function and type of procedure.

In this patient cohort, developing a model predicting the level of postoperative complications was unsuccessful. Due to considerably low prevalence of mild and severe complications, the developed model can identify only patients with no complication or moderate complication. Based on the confusion matrix, the model grouped all patients into having a no complication or moderate complication due to that reason. The accuracy, sensitivity, specificity, PPV and NPV calculated based on the confusion matrix also show that the model gives very high accuracy for patients having a mild or severe complication due to very high specificity (100% in both cases), meaning that the model never identifies patients with mild or severe complications. However, when predicting moderate complications, the model has a moderate accuracy (0.63) and low accuracy (0.58) when predicting no complications. The similar results are shown by predicted probabilities, where patients who truly have either mild or severe complications, rarely have a predicted probability that is over the threshold. Having a severe or moderate complication slightly increases the probability for patients having a moderate complication. However, regardless of which level of complication the patient truly has, the model always predicts most patients to have no complications.

The logistic EuroSCORE model predicting the level of complications performs in a similar way to the local model due to the imbalance of prevalence of different complication levels. Similarly to the local model, logistic EuroSCORE does not identify patients with either mild or severe complications, having the sensitivity of 100% for both complication levels. The accuracy for no complication and moderate complication are both lower than for the local model (0.52 and 0.61, respectively), giving a very high sensitivity for patients with no complications and very high specificity for patient with moderate complications. Similar to the local model, the predicted probability is never over the threshold for patients with mild or severe complications, and the predicted probability for having no complications is always the highest.

Chapter Nine: Discussion

In this thesis, prediction models for three outcomes were developed: (1) if the patient had a postoperative complication (yes/no), (2) if the patient had a severe postoperative complication (yes/no or other), and (3) if the patient had a higher level of postoperative complication (no/mild/moderate/severe). Local models and logistic EuroSCORE models predicting the three outcomes were developed.

9.1. Performance of the models

Based on AUC, the local model predicting severe postoperative complications has the best performance out of the local models, as shown in Table 42. In addition to being the most accurate, the model predicting severe complications has a high sensitivity, which means that the model is very good at identifying patients with severe complications. In addition, the model has a very high negative predictive value, which means that if the test is negative, the probability that patients do not have a severe complication is very high. This could help clinicians to identify patients without severe complications, in order to allocate resources accordingly.

	Postoperative complication (yes/no)		**Severe complication (yes/no or other)**	
	Local Model	Logistic EuroSCORE	Local Model	Logistic EuroSCORE
AUC	0.636	0.613	0.685	0.693
Sensitivity	65.70%	74.30%	86.90%	67.20%
Specificity	54.60%	46.50%	46.80%	63.10%

Table 42: The AUC, sensitivity and specificity for the two local models and two logistic EuroSCORE models predicting the outcomes

In terms of AUC, as visualised in Table 42, logistic EuroSCORE predicting severe postoperative complications has the best predictive ability overall (AUC=0.693), compared to the best local model (AUC= 0.685). However, the logistic EuroSCORE includes variables that are insignificant for the GJNH population when predicting postoperative complications, which will be discussed in Section 9.2.

It is difficult to compare the local models with the literature. Only five studies were found in the literature review investigating risk scores at predicting combined complications after CABG, valve and combined CABG and valve surgeries. In addition, most outcomes observed in the literature included only severe complications.

Also, the study populations may not be comparable between the studies due to possible differences in comorbidities. This highlights the need of further research of postoperative complications in cardiac patients.

The local model predicting severe complications performs better than Initial Parsonnet score in French multicentre study (AUC=0.685 vs 0.64) (Gabrielle, et al., 1997), and EuroSCORE in a single-centre study in Germany (AUC=0.685 vs 0.64) (Geissler, et al., 2000). A single-centre study in Canada shows that Initial Parsonnet score performs better than the local model (AUC=0.73 vs 0.685) (Dupuis, et al., 2001), and so does EuroSCORE in Finland (AUC=0.70 vs 0.685) (Pitkänen, et al., 2000). Cleveland Clinic score is shown to have a similar performance in Germany as the local model in GJNH population (AUC=0.69 vs 0.685) (Geissler, et al., 2000).

Compared to other studies in the literature, EuroSCORE in GJNH patient population has a relatively good performance at predicting severe complications. EuroSCORE has a similar performance in GJNH (AUC=0.693) and Finland (AUC=0.70) (Pitkänen, et al., 2000), and a slightly better performance in GJNH than in Germany (AUC=0.693 vs 0.64) (Geissler, et al., 2000), when investigating CABG, valve, and combined CABG and valve surgeries.

9.2. Small number of variables included

The local models include only seven or eight preoperative variables, whereas the logistic EuroSCORE includes fifteen variables. All variables included in the local models are routinely collected variables that are preoperatively available in most cardiac centres. Having less variables in the model makes it easier and faster to calculate and to put into use by clinicians.

Overall, as shown in Table 43, the local models include less variables than other commonly used risk scores observed in the literature review, but have similar predictive performance. All local models include age, LV function and previous MI. Variables such as extracardiac arteriopathy, unstable angina, pulmonary disease, neurological dysfunction, creatinine level and surgical priority, which are all logistic EuroSCORE variables, appeared to be insignificant in GJNH population when predicting postoperative complications.

The variables included the models will be further discussed in Section 9.3.

9.2. Large number of complications predicted

The local model predicting severe complications predicts 19 different severe complications (see Appendix C), whereas the reviewed models include only up to 13 different complications.

In the literature, if combined complications are investigated, usually only severe complications are predicted, such as bleeding, stroke, congestive cardiac failure, renal failure and deep sternal wound infection. Other outcomes that are associated with higher healthcare costs are also often investigated, such as prolonged ICU and hospital stay, ventilation time and need for inotropes.

9.3. Variables and risk factors for postoperative complications

Even though the complications observed for the local model predicting severe postoperative complications are all having a significant impact on patients' quality of life, increased hospital length of stay and healthcare costs, they all have different risk factors.

For example, age, being included in all reviewed scores and in all local models, is shown to be a risk factor for bleeding (Karthik, et al., 2004; Moulton, et al., 1996), infections (Abboud, et al., 2004; Diez, et al., 2007; Robinson, et al., 2007; Gårdlund, 2007; Cayci, et al., 2008; Harrington, et al., 2004), neurologic (Arrowsmith, et al., 2000; Roach, et al., 1996; Baranowska, et al., 2012; Gardner, et al., 2004; Reed, et al., 1988) and pulmonary complications (Bicer, et al., 2005; Hortal, et al., 2009) and renal problems (Wang, et al., 2014; Jose Olivero, et al., 2012).

However, there are some very specific variables that are risk factors for only a couple of complications. Preoperative MI is one of them, shown to be associated only with postoperative MI (Al-Attar, 2011; Livhits, et al., 2011; Koniari, et al., 2011; Yau, et al., 2008) and deep sternal wound infection (Abboud, et al., 2004; Diez, et al., 2007; Robinson, et al., 2007; Gårdlund, 2007; Cayci, et al., 2008; Harrington, et al., 2004). This could also explain why local models and commonly used risk scores do not perform outstandingly well when it comes to predicting combined complications.

There were four variables that were significant in GJNH population when analysing postoperative complications, and the severity of complications, that are not part of logistic EuroSCORE: diabetes, NYHA grade, rhythm and renal function. However, the diabetes and renal function variables are part of EuroSCORE II, Initial Parsonnet score, STS score and Cleveland Clinic score, and NYHA grade is part of EuroSCORE II. The rhythm variable is not included in the scores included in the literature review.

According to the literature review, most variables included in the local models are widely known risk factors for postoperative complications, and are also part of other commonly used risk scores that were reviewed. All models, including the local models, use age and LV function variable, which are proven to be risk factors for postoperative complications (Abboud, et al., 2004; Diez, et al., 2007; Robinson, et al., 2007; Gårdlund, 2007; Cayci, et al., 2008; Harrington, et al., 2004; Bicer, et al., 2005; Hortal, et al., 2009; Jose Olivero, et al., 2012; Gardner, et al., 2004).

Although sex variable is not included in two local models, it is included in logistic EuroSCORE, EuroSCORE II, Initial Parsonnet score and STS score. The diabetes variable is not included in logistic EuroSCORE, however is included in other reviewed scores and the local model predicting severe complications. Diabetics are shown to have higher risk of various severe complications, including congestive cardiac failure, stroke and sepsis (Arrowsmith, et al., 2000; Roach, et al., 1996; Baranowska, et al., 2012).

Active endocarditis, being part of the local model for severe complications and logistic EuroSCORE, is shown to be associated with coronary heart failure (Hasbun, et al., 2003) and acute renal failure (Conlon, et al., 1998). Amongst other reviewed commonly used scores, active endocarditis is also included in EuroSCORE II.

Other variables known to be associated with postoperative complications, included in most scores, including the local ones are having a previous myocardial infarction (MI) (Al-Attar, 2011; Livhits, et al., 2011; Koniari, et al., 2011; Yau, et al., 2008) (Abboud, et al., 2004; Diez, et al., 2007; Robinson, et al., 2007; Gårdlund, 2007; Cayci, et al., 2008; Harrington, et al., 2004), hypertension history (Arrowsmith, et al., 2000; Roach, et al., 1996; Baranowska, et al., 2012), type of procedure (Christenson, et al., 1996;

Kogan, et al., 2014; Rho, 2009; Knapik, et al., 2011), and previous cardiac surgery (Surgenor, et al., 2001; Boyer, et al., 2004; Zile, et al., 2001).

In spite of being associated with postoperative complications in the literature (Knapik, et al., 2011; Thakar, et al., 2003; Gillies, et al., 2005; Goldstone, et al., 2011; Saxena, et al., 2011), the critical preoperative state variable is only included in the local model predicting postoperative complications in general, logistic EuroSCORE and in EuroSCORE II.

Finally, only the local models predicting postoperative complications in general, and the level of postoperative complication, and EuroSCORE II include NYHA grade variable. Although, high NYHA grade is shown to be associated with gastrointestinal complications (Andersson, et al., 2005) in one study, NYHA grade has not been shown to be connected to any other complications (Raphael, et al., 2007). This shows that the NYHA grade variable needs to be investigated further.

	Complication (yes/no)	Severe complication (yes/no or other)	Complication level (no/mild/moderate/severe)	Designed to predict mortality			Designed to predict mortality and morbidity	
	Local Model	Local Model	Local Model	Logistic EuroSCORE	EuroSCORE II	Initial Parsonnet	STS	Cleveland Clinic
Patient characteristics								
Age	x	x	x	x	x	x	x	x
Sex		x		x	x	x	x	
Diabetes		x			x	x	x	x
BMI						x	x	x
Race							x	
Cardiac variables								
Extracardiac arteriopathy				x	x			
Active endocarditis		x		x	x			
Angina status				x	x		x	
LV function	x	x	x	x	x	x	x	x
Previous MI	x	x	x	x	x		x	
Hypertension history		x		x	x			
NYHA grade	x		x		x			
Rhythm	x		x					
Preoperative IABP						x	x	
Peripheral vascular disease							x	x
Non-cardiac variables								
Pulmonary disease				x	x	x	x	x
Neurological dysfunction				x	x		x	x
Renal function	x		x		x	x	x	x
Creatinine level				x				
Surgery								
Surgical priority				x	x	x	x	x
Procedure	x		x	x	x	x	x	x
Critical preoperative state	x			x	x			
Previous cardiac surgery		x		x	x	x	x	x
Number of variables	**8**	**8**	**7**	**15**	**17**	**11**	**16**	**11**

Table 43: The comparison between included variables in the three local models, logistic EuroSCORE, EuroSCORE II, Initial Parsonnet score, Cleveland Clinic score and STS score

9.4. Limitations of the data

9.4.1. Reporting of postoperative complications

The reporting of postoperative complications in the database might have some limitations. Everything reported in the database is based on the clinicians' notes, which are reviewed by database managers. It is not known how vigilantly the postoperative complications were recorded.

For some patients very detailed complications were reported, but it is possible that only more common complications were reported for most patients. As stated in Chapter Six, most patients (25.78%) had only one complication, 11.90% had two complications, and 10.97% of the patients had three or more complications. Some complications include a disease, some include only the action taken to cure the disease, without disease being reported.

For example, 13.73% of the patients had the use of inotropes as a postoperative complication. However, the use of inotropes by itself is not a postoperative complication, but is an action taken to cure the postoperative complication. The use of intra-aortic balloon pump (IABP) was often accompanied with reasons of use, which was mainly either unstable angina or haemodynamic instability, which are the actual postoperative complications. However, there is no additional information on why exactly inotropes were used, why the patient was re-ventilated, minitracheostomy, impeller device, and continuous positive airway pressure (CPAP) was required. Although, reporting the use of support tools are helpful when it comes to economic evaluation of postoperative care, more exact reporting is needed for the complications.

9.4.2. Inconsistently reported variables

In CaTHI database, only logistic EuroSCORE variables were consistently available, which means that some variables that could be associated with postoperative complications in GJNH population were missed. In particular, renal impairment and haemoglobin levels are important variables that were not consistently filled in.

The literature has shown that renal impairment is associated with low cardiac output, bleeding and prolonged ventilation after surgery (Al-Sarraf, et al., 2011). Renal complications are a major complication (Bove, et al., 2009; Jose Olivero, et al., 2012), and therefore measuring renal function before surgery is crucial to prevent patients having postoperative renal problems. In the logistic EuroSCORE model, the renal function is measured with creatinine level, which is consistently recorded in the CaTHI database, however there is no alternative for measuring haemoglobin levels.

9.4.3. Only preoperative information available

The models predicting postoperative complications and the level of postoperative complications included the rhythm variable. According to the models, patients with a sinus rhythm are more likely to have postoperative complications, or a higher level of complications than patients with an abnormal rhythm. This is a very surprising result as it is unexpected that a patient with a normal rhythm should have a higher risk of postoperative complications.

We do know that the rhythm variable is recorded accurately due to being recorded based on electrocardiogram (ECG) undertaken during preoperative assessment. However, as the data was collected during preoperative assessment, we only know the rhythm recorded during that time, without having information about arrhythmia problems in the past. The most prevalent postoperative complication was atrial fibrillation (28.41%), which could be largely affected by past problems with rhythm, which is shown to be a risk factor for postoperative atrial fibrillation in the literature (Alqahtani, 2010; Banach, et al., 2006; Mathew, et al., 2004).

9.4.4. Recommendations

Firstly, in order to make the reporting of postoperative complications more exact and consistent, a coding system could be put into use. One option could be the use of ICD-10 codes. However, many postoperative complications do not have an exact ICD-10 code. This highlights the need of further research in postoperative complications.

Having a more streamlined way of reporting helps making the surveillance of postoperative complications easier and more transparent, making the research of postoperative complications more consistent. In addition, a separate way of reporting the treatment for postoperative complications could help calculating healthcare costs increased by postoperative complications.

Secondly, the risk factors included in the local model predicting severe postoperative complications could be included as a mandatory field in the CaTHI database in order to improve a future evaluation of the model. The new mandatory variables could be diabetes, haemoglobin levels and if the patient has had any past arrhythmias.

9.5. Limitations of the models

9.5.1. Low specificity and positive predictive value

All three local models have a considerably low specificity, meaning that the models are not very good at identifying patients without severe complications. However, this is a problem also for the logistic EuroSCORE models predicting the three outcomes.

A test with a lower specificity has a higher type I error rate, meaning, that according to the test, a patient can have a severe postoperative complication, when in fact, they do not. Although, both high sensitivity and specificity are looked for, it is often not possible due to a trade-off between sensitivity and specificity.

In addition to the low specificity, the local model and logistic EuroSCORE model predicting severe complications have very low positive predictive values. This is due to the fact that the prevalence of severe complications is very low, which affects the predictive values.

The performance of the models could be affected by the fact that even though the complications observed for the local model predicting severe postoperative complications are all having similar impact on patients and healthcare after surgery, they all have different risk factors. For example, some variables are risk factors for only a couple, but very severe postoperative complications, further discussed previously in Section 9.3.

9.5.2. Postoperative complications and the level of complications

Although the local model and logistic EuroSCORE model predicting postoperative complications have a moderate performance, they do not have the ability to identify the severity of complication. Patients with a mild postoperative complication might not require special attention, whereas with moderate and severe complications do, and therefore using a model that predicts complications in general does not offer much information about high risk patients.

In order to solve that problem, models predicting the level of postoperative complications were developed. However, neither local model nor logistic EuroSCORE model were successful for that outcome due to the fact that the prevalence for mild and severe complications was very low. This resulted the models never identifying patients with mild or severe complications.

9.5.3. Single-centre study

Finally, this is a single-centre study, meaning that the models developed are applicable for Golden Jubilee National Hospital cardiac patients only. However, the GJNH patients can be from all over Scotland, and more than 50% of cardiac procedures take place in there. Therefore, it is possible that the developed models could be applied in Scottish cardiac centres in general.

Chapter Ten: Conclusion

As a conclusion, this thesis offers a general contribution to the research of postoperative complications following cardiac surgery. The variables associated with postoperative complications could help clinicians understand which patients are more likely to have severe complications in order to offer those patients more attention.

If the hospital uses logistic EuroSCORE as a preoperative risk stratification tool, it could be also taken into account that patients with a higher logistic EuroSCORE are more likely to have severe postoperative complications than patients with a lower logistic EuroSCORE.

The local model predicting severe postoperative complications, having the best performance out of the local models, has a similar performance to commonly used risk scores in the literature, however includes only eight variables that are all already routinely collected preoperatively available variables. The model could help clinicians to identify patients without severe complications in order to allocate resources accordingly.

10.1. Original Contribution

With mortality being the most commonly reported outcome when evaluating risk scores, this thesis offers a contribution to the understanding of postoperative morbidity and the risk factors for postoperative complications after cardiac surgery. The thesis identified variables associated with postoperative complications, and therefore provided a starting point for establishing a prediction model in clinical practice. It is of benefit to clinicians, policy-makers and healthcare analysts by contributing to a model development and evidence that could be used in a clinical setting to identify patients with potential postoperative complications.

The thesis shows how a commonly used cardiac risk of mortality tool logistic EuroSCORE performs at predicting postoperative complications, and it could be used in identifying patients with possible postoperative complications.

This is the first model predicting postoperative complications that has been developed to use in Golden Jubilee National Hospital.

10.2. Future work

This thesis is the initial step for developing a prediction model for clinical practice. In order to implement the local model predicting severe postoperative complications in Golden Jubilee National Hospital, a validation study and impact analysis need to be undertaken. To confirm that predictors are accurate outside the original data set, a prospective study could be undertaken at the Golden Jubilee National Hospital.

There are various ways to improve the models developed in this study. Different machine learning methods could be used. For example, bagging, boosting and stacking could all improve the models' predictive ability. Also, different algorithms could be used, such as Random Forest or k-Nearest Neighbours, to name a few. In addition, using logistic regression with GAM could improve the performance of the model.

As mentioned several times throughout the thesis, postoperative complications are proven to increase hospital length of stay. It could be also investigated how the local models predict hospital length of stay, ICU stay, and even healthcare costs.

In order to make the use of the local model more accessible, a mobile or web-based application could be built that could highlight patients who are more likely to have severe complications in order to help clinicians at decision making.

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A. List of procedures

CABG procedures	Population (%)	Valve procedures	Population (%)
CABG:3	1150 (31.1%)	Aortic	886 (23.9%)
CABG:4	493 (13.3%)	Aortic (MIS)	51 (1.4%)
CABG:2	402 (10.9%)	Aortic Redo	39 (1.1%)
CABG:3 (OPCAB)	54 (1.5%)	Aortic (Converted MIS)	4 (0.1%)
CABG:2 (OPCAB)	41 (1.1%)	**Combined procedures**	**Population (%)**
CABG:5	26 (0.7%)	Aortic; CABG	215 (5.8%)
CABG	21 (0.6%)	Aortic; CABG:2	171 (4.6%)
CABG:4 (OPCAB)	7 (0.2%)	Aortic; CABG:3	106 (2.9%)
CABG Redo:3	4 (0.1%)	Aortic; CABG:4	12 (0.3%)
CABG:6	3 (0.1%)	Aortic Redo; CABG	4 (0.1%)
CABG Redo	3 (0.1%)	Aortic; CABG Redo	3 (0.1%)
CABG Redo:4	2 (0.1%)	Aortic; CABG Redo:2	1 (0.0%)
CABG Redo:2	1 (0.0%)	Aortic; CABG:5	1 (0.0%)

B. List of variables

Variable	Description	Completeness
Age	Patient's age in years	100%
Sex	Patient's gender (Male/Female)	100%
Diabetes	If the patient has diabetes (Yes/No)	100%
Body Mass Index (BMI)	Patient's BMI: Underweight (<18.5), Normal (18.5-24.9), Overweight (25.0-29.9), Obese (>30.0)	100%
Smoking Status	Patient's smoking status (Never smoked/Current smoker/Ex-smoker/Unknown)	63.76%
Neurological dysfunction	If the patient has neurological dysfunction (Yes/No)	100%
Pulmonary disease	If the patient has a pulmonary disease (yes/No)	100%
Congestive cardiac failure	If the patient has had a congestive cardiac failure (At admission/Past/Never)	100%
Previous myocardial infarction (MI)	If the patient has had a previous myocardial infarction (Yes/No)	100%
Active endocarditis	If the patient has active endocarditis (Yes/No)	100%
Hypertension history	If the patient has had hypertension (Yes/No)	100%
Pre-operative serum creatinine	Creatinine level before surgery (<200 µmol/ L or ≥ 200 µmol/ L)	100%
NYHA grade	New York Heart Association classification	100%
Angina Status	Angina status classification	100%
Rhythm	Patient's rhythm of the heart (Sinus/Abnormal/Unknown)	92.03%
Left ventricular (LV) Function	Patient's left ventricular function (Good/Moderate/Poor)	100%
Renal impairment	Patient's renal function (Normal/Moderate/Severely impaired/Unknown)	56.62%
Left main stem (LMS)	If the patient has a left main stem disease (No LMS disease/LMS disease/Unknown)	51.24%
Extracardiac arteriopathy	If the patient has extracardiac arteriopathy (Yes/No)	100%
Surgical priority	Patient's surgical priority (Elective/Emergency/Urgent/Prioritised)	100%
Critical preoperative state	If the patient is in a critical state (Yes/No)	100%
Procedure	Surgical procedure (CABG/Aortic Valve/Combined CABG and Aortic Valve)	100%
Previous cardiac surgery	If the patient has had cardiac surgery before (Yes/No)	100%
Previous percutaneous coronary intervention (PCI)	If the patient has had percutaneous coronary intervention before (Yes/No)	100%
Postoperative complication	If the patient has complications after surgery (No/Mild/Moderate/Severe)	100%
Outcome	Outcome at the end of admission (Dead/Alive)	100%
Postoperative ventilation hours	How long the patient is under ventilation after surgery in hours	100%
Total days in hospital	How long does the patient stay in the hospital in days	100%
Intensive care unit (ICU) hours	How long does the patient stay in the ICU in hours	100%
Logistic EuroSCORE	Preoperatively calculated logistic EuroSCORE reported in CaTHI	100%
APACHE II score	APACHE II score calculated at the admission to the ICU reported in CaTHI	100%

C. List of postoperative complications

Severe complication	Occurrence (95% CI)
Acute renal failure	1.59% (1.24-2.05)
Deep sternal wound infection	1.27% (0.96-1.68)
Septicaemia	1.11% (0.82-1.50)
Transient stroke	0.78% (0.55-1.12)
Percutaneous tracheostomy	0.76% (0.52-1.09)
Cardiac arrest	0.73% (0.50-1.06)
Permanent stroke	0.51% (0.33-0.80)
Severe heart failure	0.51% (0.33-0.80)
Adult respiratory distress syndrome	0.32% (0.19-0.57)
Multi-organ failure	0.27% (0.15-0.50)
Mesenteric infarction	0.27% (0.15-0.50)
Required laparotomy	0.24% (0.13-0.46)
Severe pulmonary oedema	0.16% (0.07-0.35)
Left ventricular wall dissection	0.11% (0.04-0.28)
Hepatic failure	0.08% (0.03-0.24)
Reopening requiring CABG	0.08% (0.03-0.24)
Paraparesis	0.03% (0.00-0.15)
Amputation	0.03% (0.00-0.15)
Open tracheostomy	0.03% (0.00-0.15)

Moderate complication	Occurrence (95% CI)
Atrial Fibrillation	28.41% (26.98-29.88)
Return to the theatre	5.19% (4.52-5.95)
Pulmonary Infection Requiring Antibiotics	4.92% (4.27-5.66)
Postoperative Elevated Creatinine	3.51% (2.97-4.16)
Intra-aortic Balloon Pump Used	3.03% (2.52-3.63)
Sternal Wound Leak	1.86% (1.48-2.35)
Other Respiratory Complication	1.73% (1.36-2.20)
Re-ventilated	1.57% (1.21-2.02)
Nasogastric Feeding	1.54% (1.19-1.99)
Permanent Pacemaker	1.35% (1.03-1.78)
Superficial Wound Infection	0.81% (0.57-1.16)
Leg Wound Leak	0.81% (0.57-1.16)
Low Cardiac Output	0.76% (0.52-1.09)
Psychosis Requiring Treatment	0.73% (0.50-1.06)
Ventricular Fibrillation/Tachycardia	0.70% (0.48-1.03)
Urinary Tract Infection	0.65% (0.44-0.96)
Pacing Dependence Delaying Discharge	0.59% (0.39-0.90)
Haemothorax Requiring Drain	0.57% (0.37-0.87)
Other CNS Complication	0.54% (0.35-0.83)

Leg Wound Infection	0.54% (0.35-0.83)
Sternal Dehiscence	0.51% (0.33-0.80)
Prolonged ileus	0.46% (0.29-0.73)
Unstable angina	0.41% (0.25-0.67)
TPN	0.32% (0.19-0.57)
Bleeding Peptic Ulceration	0.27% (0.15-0.50)
Other Renal Complication	0.19% (0.09-0.39)
Perioperative Myocardial Infarction	0.19% (0.09-0.39)
Minitracheostomy	0.16% (0.07-0.35)
Thigh Wound Leak	0.16% (0.07-0.35)
Femoral Wound Infection	0.11% (0.04-0.28)
Delayed Sternal Closure	0.05% (0.01-0.20)
Fasciotomy	0.05% (0.01-0.20)
Femoral Artery Embolectomy	0.05% (0.01-0.20)
Heel Pressure Sore	0.05% (0.01-0.20)
Leg wound dehiscence	0.05% (0.01-0.20)
Paravalve Leak	0.05% (0.01-0.20)
thigh wound infection	0.05% (0.01-0.20)
Acute Cholecystitis	0.05% (0.01-0.20)
Impeller Device Used	0.05% (0.01-0.20)
Ischaemic Limb	0.03% (0.00-0.15)
Sacral Pressure Sore	0.03% (0.00-0.15)
Secondary Haemorrhage	0.03% (0.00-0.15)

Mild complication	**Occurrence (95% CI)**
Inotropes	13.73% (12.66-14.88)
Required CPAP	8.97% (8.09-9.94)
Haemodynamic instability	2.32% (1.89-2.86)
Cardioverted	2.03% (1.62-2.53)
Social Circumstance Delaying Discharge	0.81% (0.57-1.16)
Other Miscellaneous Complication	0.73% (0.50-1.06)
Other GI Tract Complication	0.49% (0.31-0.77)
Pyrexia of Unknown Origin	0.46% (0.29-0.73)
Low Systemic Vascular Resistance State	0.38% (0.23-0.63)
Other Cardiac Complication	0.38% (0.23-0.63)
Sternal Resuturing	0.32% (0.19-0.57)
Urinary Retention	0.32% (0.19-0.57)
Defibrillated	0.27% (0.15-0.50)
Other Atrial Arrhythmia	0.19% (0.09-0.39)
Other Wound Complication	0.19% (0.09-0.39)
Other Peripheral Vascular Complication	0.14% (0.06-0.32)
Other Support Device Used	0.05% (0.01-0.20)