CHEST PAIN IN EMERGENCY DEPARTMENT PATIENTS: A COMPARISON OF LOGISTIC REGRESSION VERSUS MACHINE LEARNING IN PREDICTING MAJOR ADVERSE CARDIAC EVENTS AND ABNORMAL TROPONIN

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ABSTRACT

Myocardial infarction is the primary diagnosis to rule out in emergency department chest pain patients. In this retrospective, multi-site study, we compared logistic regression (LR) with machine learning (ML) in predicting which patients were at risk of major adverse cardiac events (MACE) and abnormal troponin. Of the 1,538 patients identified over 43 days, 1,014 were retained of whom 70 suffered a MACE. LR and ML models for MACE were internally validated and achieved similar area under curve (AUC): 0.89 (95% CI: 0.87, 0.93) and 0.92 (95% CI: 0.89, 0.94) respectively. Abnormal troponin models had overlapping AUCs. Two novel clinical decision scores were derived: the Preliminary Chest Pain Risk Score with a sensitivity of 100.00% (95% CI: 94.87%, 100.00%) for identifying low risk chest pain patients and the Ultra-Low Risk Troponin Score which could be used in lieu of troponin. Future prospective studies will be required to externally validate these scores.

EXECUTIVE SUMMARY

CONTEXT: Chest pain is the second most common presenting complaint in patients presenting to the emergency department (ED). Myocardial infarction (MI) is the main diagnosis to rule out in chest pain patients. MI rapid diagnosis and treatment is required to limit morbidity and mortality.

OBJECTIVES: Our primary objective was to compare logistic regression (LR) with machine learning (ML) in predicting which patients were at risk of major adverse cardiac events (MACE) and an abnormal troponin. Our secondary objective was to create clinical decision scores (CDS) for MACE and abnormal troponin based on the multivariable LR models developed. **DESIGN & SETTING:** We designed a retrospective cohort study enrolling atraumatic chest pain patients at the EDs of the Civic Hospital and General Hospital in Ottawa, Ontario from November 27th 2019 to January 8th 2020.

SUBJECTS: Adults (≥18 years of age), presenting with a primary complaint of chest pain to the ED and having an electrocardiogram (ECG) or high-sensitivity troponin drawn on the visit were enrolled. We excluded patients who: were < 18 years of age, did not have a troponin drawn or ECG done, had traumatic chest pain, were diagnosed ST-elevation myocardial infarct (STEMI) prior to or on immediate arrival to the ED, were transferred from another hospital, left unseen by the physician, had a stress test or angiogram within 1 month of the ED visit, had a cardiac procedure/surgery within 1 month of the ED visit or resided outside the Ottawa area.

DATA COLLECTION: Data on patient demographics, initial ED course, past medical history, medication history, vital signs, history of presenting illness, ECG characteristics, troponin values, coronary angiogram results performed on index ED visit and final diagnoses were obtained from patients' individual electronic charts by one of four data abstractors.

DATA ANALYSIS: Continuous variables were reported by means, medians, standard deviations & ranges. Categorical or dichotomous variables were described using frequencies and percentages. Continuous variables were transformed into dichotomous variables with clinically significant cut-offs before building multivariable LR models using backward elimination. LR models were internally validated using bootstrapping. ML random forest modelling was done according to specific instructions, in isolation without knowledge of the LR models.

OUTCOME MEASURES: We used a composite outcome of MACE within 6 weeks of index ED visit. The seven-point MACE composite outcome included: acute MI, ischemic stroke, cardiovascular death, revascularization (percutaneous coronary intervention or coronary artery bypass grafting), unstable angina, ventricular arrhythmia (sustained ventricular tachycardia or fibrillation) secondary to a blocked coronary and cardiac arrest. Outcomes were verified by searching the electronic medical records of our institution.

RESULTS: Of the 1,538 patients presenting with chest pain over 43 consecutive days, 1,014 patients were retained of whom 70 suffered a MACE. Internally validated LR and ML models for MACE achieved similar area under curve (AUC): 0.89 (95% CI: 0.87, 0.93) and 0.92 (95% CI: 0.89, 0.94) respectively. Abnormal troponin models had overlapping AUCs. Two novel CDS were derived: the Preliminary Chest Pain Risk Score with a sensitivity of 100.00% (95% CI: 94.87%, 100.00%), a specificity of 47.67% (95% CI: 44.44%, 50.91%) for identifying low risk chest pain patients and the Ultra-Low Risk Troponin Score which could be used in lieu of troponin in certain patients and could have eliminated the need for troponin testing in 10.8% of patients in our study.

CONCLUSION: LR and ML both yielded excellent models at predicting MACE or abnormal troponin. Future prospective studies will be required to externally validate the clinical decision scores that were derived.

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CHAPTER 1: INTRODUCTION

1.1 INTRODUCTION TO THE PROBLEM

Chest pain accounts for 5-7% of all emergency department (ED) visits and 5-20% of all hospital admission from the ED. [1-3] While the majority of patients with chest pain are diagnosed with a non-life-threatening diagnosis such as musculoskeletal pain, costochondritis or reflux, the role of the ED physician is to rule out certain life-threatening diagnoses facilitating their safe discharge from the hospital however this can be a timely process. [4] According to the Canadian Institute for Health Information between April 2021 and March 2022, patients presenting with *pain in throat and chest*, the second most common ED presenting complaint nationwide, spent an average of 8 hours in the ED and only 2% of patients with this presentation were admitted to the hospital. [5]

Heart attacks, medically referred to as acute coronary syndromes (ACS), are one of the main diagnoses to rule out as these are associated with increased morbidity and mortality not only on index ED visit but also in the years following the diagnosis. [6] It has been reported that 18% of men and 23% of women over the age of 40 who suffer from ACS will die within 1 year of the event. [7] Ischemia of the heart can be complicated by life-threatening arrhythmias, heart failure, strokes or death. [8]

The diagnosis of ACS relies on history, electrocardiogram (ECG) findings and laboratory testing. However, accurately diagnosing ACS in patients with chest pain can be challenging due to atypical presentations and multiple human and resource factors explaining the missed ACS diagnosis rate of 1-2% quoted in literature. [9] Clinical decision scores have recently been developed to help the physician diagnose the undifferentiated chest pain patient but have some shortfalls. These scores have been constructed using traditional statistical techniques such as linear

and logistic regression which rely on the researcher to derive the score by selecting ahead of time a limited number of variables of interest expected to be related to the outcome. Existing knowledge of causal relationships between predictors and outcomes can bias model building when using these techniques. In contrast, modern machine learning techniques have greater computing power facilitating the processing of a larger amount of data while accounting for complex interactions between a greater number of predictor variables. [10] Moreover, despite a few published scores on the risk of ACS in patients that present to the ED, no scores have been developed to predict which patient will have a positive blood test result indicating possible ischemia. [11, 12]

1.2 ACUTE CORONARY SYNDROME

1.2.1 Acute Coronary Syndrome Pathophysiology

In 80% of cases, ACS is caused by thrombosis of the coronary arteries supplying the heart. [13] Other causes of ACS include coronary spasm (Prinzmetal angina), embolism, dissection, trauma or low-flow states such as anemia or hypotension. Atherosclerosis or the hardening of arteries precedes the thrombotic event and is accelerated by micro-vascular trauma secondary to such things as smoking or hypertension. Plaque buildup occurs at the site of vessel damage and elevated lipid levels (cholesterol and triglycerides) will favour growth of the plaques leading to inflammation, fibrin deposition and eventual coronary artery lumen narrowing. These plaques can partially impede blood flow and cause a small myocardial infarction (MI), also referred by patients as a “minor” heart attack. Their rupture can cause complete occlusion of the coronary artery preventing oxygen-rich blood from reaching the cardiac muscle ultimately leading to myocardial cell oxygen starvation in turn leading to a large MI, arrhythmias (ventricular tachycardia or fibrillation) or structural heart damage, both of which lead to cardiac pump failure and the cessation of the supply of oxygenated blood throughout the body.

1.2.2 Acute Coronary Syndrome Classification and Diagnosis

ACS can be classified as ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMIs) and unstable angina (UA). STEMIs are relatively straightforward to diagnose on an ECG as they are caused by complete obstruction of blood flow to a large area of the heart which leads to changes in the electrical activity of those cells that can easily be detected. A STEMI diagnosis does not require any bloodwork and ECG diagnostic criteria has been published most recently in 2018:

Fourth Universal Definition of Myocardial Infarction:
STEMI Diagnosis ECG Criteria [14]

New ST-elevation at the J-point in 2 contiguous leads with the cut-point:

1. ≥1 mm in all leads other than leads V_2–V_3
2. ≥2 mm in leads V_2–V_3 in men ≥40 years or ≥2.5 mm in leads V_2–V_3 men <40 years
3. ≥1.5 mm in leads V_2–V_3 in women regardless of age

Correctly identifying patients with NSTEMIs or UA is more challenging however as the diagnosis cannot be made exclusively by ECG interpretation. NSTEMIs are caused by partial obstruction in blood flow and as such the area of the heart affected is smaller leading to more subtle ECG changes such as ST depressions or T-wave inversions. In certain instances, an NSTEMI can occur without any ECG changes. A study reporting on missed MIs has shown that 53% of patients with a missed NSTEMI were found to have normal/nondiagnostic ECGs. [15] The diagnosis of NSTEMI is thus more difficult and requires a detailed history, physical exam and laboratory results for troponin, a cardiac-specific protein. NSTEMI diagnosis can therefore be delayed by the drawing of blood, the processing of the troponin test in the laboratory and inconclusive ECGs/troponin values. The diagnostic criteria of an NSTEMI due to plaque thrombosis/embolism has also been published most recently in 2018:

Fourth Universal Definition of Myocardial Infarction:
Criteria for Type 1 Myocardial Infarction [14]

Detection of a rise and/or fall of elevated cardiac troponin values with at least 1 value above the 99th percentile upper reference limit and one of the following:

a. Acute MI symptoms
b. New ischemic changes or new pathological Q waves on ECG
c. New loss of viable myocardium or regional wall motion abnormality on imaging which can be explained by an ischemic etiology
d. Coronary thrombus identified by angiography or autopsy

The diagnosis of UA is even more challenging as by definition, unlike with STEMI and NSTEMI where there is cellular death, there is no infarction with this type of ACS but only reversible ischemia (oxygen starvation). As such, the ECG may show even more subtle changes (if any) and the troponin is normal as there is no cell death. Thus, the diagnosis of UA often relies on the history provided by the patient. The prompt diagnosis of this type of ACS is particularly important as it can quickly evolve into a NSTEMI or STEMI if left untreated.

The time to diagnosis and treatment of any type of ACS following symptom onset is crucial as delays are known to be associated with worse outcomes. [16] In fact, up to 70% of patients suffering from ACS will die before they reach medical care in a hospital or other health-care setting. [17]

1.2.3 Troponin Testing

In the last 50 years, NSTEMI diagnosis has always relied on some form of laboratory testing for enzymes released by the myocardium during myocyte death. [18] Aspartate aminotransferase (AST) and creatine kinase (CK) which are also present in skeletal muscle tissue were originally measured. They were eventually replaced by the cardiac-specific troponin enzyme testing which is now used as a standard of care in the work-up of chest pain patients with possible ACS. Attesting to their utility in the diagnosis of MI, an elevated troponin is now also part of the

universal definition of MI. [19] However, due to the time required for the troponin enzyme to be detected in the blood after an MI, troponin frequently requires serial measurements at pre-determined time frames, multiple hours apart, after presentation. [20]

Since the introduction of the first widely available troponin test in the 1990s, multiple assays have been made available with increasing sensitivity for MI and in 2010 high-sensitivity troponin (hs-Trop) became available. [18] These newer hs-Trop assays with improved sensitivity over the conventional troponin assays' intermediate sensitivity, have allowed for the more rapid detection of the enzyme in the blood. They have paved the way for the shorter 0/1 hour troponin protocol in lieu of the previously established 0/3/6 hour conventional troponin assay protocols. [21] Single-troponin testing in patients with very low troponin results, regardless of symptom onset, has also been gaining approval thanks to the improved detection of the hs-Trop assays. [22] However, since a range of other conditions not related to cardiac ischemia can elevate the troponin such as pulmonary embolism, renal disease, pericarditis or myocarditis, heart failure, sepsis or even strenuous exercise, patients often require more than one troponin to be drawn to rule out MI resulting in long ED length of stay for chest pain patients. [23] In fact, the length of stay is so long that dedicated chest pain units have been set up in certain countries to help decant chest pain patients from the ED and reduce health care costs. [24]

There is also increasing evidence that sex should be taken into account when determining the appropriate cut-off for an abnormal troponin suggestive of ischemia. Due to body composition, cardiac physiology and the effects of estrogen, women have been found to have lower levels of the troponin enzyme. [25] This has been suggested to be one of the reasons that they experience a higher chest pain misdiagnosis rate when compared with men. [26] Recently it has been shown that sex specific diagnostic thresholds can help remedy this issue and double the diagnosis rate of MI in women. [27]

Although the advent of troponin testing has aided clinicians to more promptly diagnose ACS, there are commonly long delays in drawing bloodwork and obtaining troponin results due to human resource factors, scarcity of equipment and the time it takes for analysis in the laboratory. It is in fact recommended to avoid waiting for a troponin test result before providing urgent cardiology care in patients that are deemed to be at high risk based on risk factors and symptom characteristics. [28]

1.2.4 Acute Coronary Syndrome Treatment

ACS is typically treated with a combination of medical therapy and revascularization. Medical therapy includes the use of anti-platelets (aspirin or clopidogrel or ticagrelor) alongside medications that reduce cardiac demand (beta-blockers) or those that reduce cardiac remodelling following myocardial infarction (angiotensin-converting enzyme/ACE inhibitors). Once the acute phase of the ACS event has occurred, medical therapy also involves the treatment of conditions that could have precipitated the ACS such as hypertension and cholesterol.

Revascularization therapy often takes the form of non-invasive techniques such as radial or femoral artery percutaneous coronary intervention (PCI) using an inflated balloon alone to open up a previously occluded coronary artery or by also inserting either a bare-metal or medication-eluting stent to keep the obstruction from re-forming. In instances where there is either a high-grade blockage in one or more major coronary arteries or in which PCI failed, revascularization can be achieved by a more invasive technique known as coronary artery bypass grafting (CABG) which grafts a vein in parallel to a blocked coronary artery allowing for the alternative transit of oxygenated blood to the myocardium. [29]

1.2.5 Epidemiology of Acute Coronary Syndrome

With an estimated 17.8 million annual deaths, cardiovascular diseases are the leading cause of death worldwide. [30] In Canada, there were 21,000 deaths from ACS in 2009 and it is estimated that every 5 minutes a patient is admitted to the hospital with ACS or chest pain totalling 100,000 annual hospitalizations. [31] Roughly 2.4 million Canadians or 8.5% of the population over the age of 20 has been diagnosed with ischemic heart disease and 578,000 (2.1%) have been previously diagnosed with an MI. [32] The incidence of ischemic heart disease is 6.1 per 1,000 adults per year while the incidence of MI is 2.3 per 1,000 adults per year. [32]

1.2.6 Acute Coronary Syndrome Risk Factors

Atherosclerosis and consequently ACS risk factors have been well described in literature, most comprehensively, by the original Framingham Heart study which enrolled and followed two-thirds of the population of a small city (5,209 participants) over multiple years publishing its results for the first time in 1957. The study classified MI risk factors into non-modifiable risk factors (age, sex) and modifiable risk factors (hypertension, high cholesterol). [33]

Age is the most important non-modifiable risk factor for ACS as patients aged 65-74 have been shown to have seven times the incidence of ACS compared with those aged 35-44. [34] Sex meanwhile has smaller effects on the incidence of ACS and these tend to decrease with advanced age. More specifically, men have been shown to have 2.5-3 times greater incidence of ACS when compared with women however this sex difference is no longer apparent after the age of 55. [35, 36]

Interestingly, women with ACS have been shown to present with different symptoms than those experienced by men. For example, they are less likely to present with chest pain or diaphoresis and are more likely to present with pain between the shoulder blades, nausea or

vomiting and shortness of breath. [37] In fact, in a multi-site study enrolling women recently diagnosed with an acute MI, only 29.7% presented with chest pain while many more were found to have atypical symptoms such as fatigue (70.7%) and sleep disturbance (47.8%) preceding their MI. [38]

In terms of the most important modifiable risk factors, the most comprehensive report is from the 2004 study titled *Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries* (INTERHEART study). The case-control study used data from 15,152 patients admitted with ACS in 52 countries and reported on 6 different modifiable risk factors. The following risk factors were all found to be statistically significant: active smoking, dyslipidemia, hypertension, diabetes, obesity, premature family history of coronary disease. [39]

In addition to these, non-traditional risk factors have recently been described in the literature as increasing the risk of atherosclerotic disease. These include pregnancy, human immunodeficiency virus (HIV) infection, vasculitides and alcohol use. [40]

1.2.7 Major Adverse Cardiac Events

Major adverse cardiac events (MACE) is a term commonly encountered in cardiology and emergency medicine literature to describe clinically relevant and serious cardiovascular events. The term was first used in 2008 by the United States Food and Medication Administration (FDA) to standardize outcomes in clinical trials reporting on the cardiovascular safety of medications to treat diabetes. [41] The composite outcome initially only included acute MI, stroke and cardiovascular mortality. Additional studies in cardiology and emergency medicine expanded MACE to include other clinically relevant outcomes such as revascularization (PCI, CABG), cardiogenic shock, arrhythmias, and cardiac arrest. The time-frame for MACE that is used in emergency medicine literature is highly variable but most commonly is 30-days or 6-weeks

following the index ED visit. The short time frame is preferable in the specialty as it focuses on acute life-threatening presentations. To this date, there is no universal definition of MACE.

1.3 CLINICAL DECISION SCORES

1.3.1 Development and Use of Clinical Decision Scores in the ED

Clinical decision scores (CDS) have been steadily growing in popularity and use in the ED. They remedy some of the diagnostic challenges that exist in the ED secondary to the fast-paced, often disorganized environment staffed by sleep-deprived shift-workers. [42]

The Ottawa ankle rules, the first widely-used CDS, was developed more than 25 years ago. [43] The rule allows for the systematic assessment of ankle injuries to determine which patients were at highest risk of having a fracture and would benefit from an x-ray. Since then, a number of rules for a range of presentations from head injury to syncope have been prospectively validated with the ultimate goal of reducing diagnostic error. [44] Rules have standardized care across provincial and national boundaries while reducing unnecessary testing. For example, systematically using the pulmonary embolism rule-out criteria (PERC) rule in patients with suspected pulmonary embolism can lead to a reduction of D-dimer testing by almost a third. [45] Similarly, the use of the Canadian C-spine rules in the work-up of trauma patients with neck pain can reduce imaging rates by 45%. [46]

Other robustly derived and validated CDS have meanwhile failed to show a clinical impact. For example, a multi-site knowledge-translation-based trial of the Canadian Computerized Tomography (CT) Head rule, initially derived to indicate which blunt head trauma patients should be imaged with a CT Head, did not show a reduction in the rates of CT head imaging in the period following the implementation of the CDS. [47] The education initiatives at the implementation

sites of this study (one-hour teaching session, posters, pocket cards and study distribution) actually had the opposite effect and increased the rates of imaging from 62.8% pre-intervention to 76.2% post-intervention although this was not found to be a statistically significant (difference +13.3%, 95% CI: 9.7%–17.0%).

1.3.2 Clinical Decision Score Methodology

Methodological standards for the creation of CDS are well documented. There are 6 important stages in the creation of a CDS as described by Stiell & Wells. [48] The stages are as follows:

1. Determine if there is a need for a CDS.

2. Build the CDS according to rigorous methodological standards.

3. Once the CDS has been created, validate it prospectively in a new group of patients.

4. Implement the CDS into clinical practice and demonstrate its effect on patient care or resource utilization or both.

5. Perform a cost-effectiveness analysis of the CDS.

6. Ensure efficient and effective dissemination of the CDS.

Stiell & Wells describe these stages in detail. [48]. Stage 1 is a formal needs assessment for a CDS and can be broken down further by answering questions about the prevalence of the condition, the current diagnostic test in use, variation in clinical practice, attitudes of the physician regarding unnecessary testing for the condition and the current clinical accuracy of physicians. Stage 2 is the actual derivation of the CDS and includes important aspects such as defining reliable predictors and an outcome, selecting the appropriate patients, ensuring that the sample size is

adequate, using mathematically sound techniques and ensuring that the sensibility and accuracy of the CDS are sufficiently high.

The ideal CDS would involve a presentation or disease that is either highly prevalent or requires extensive resource utilization so as to have the greatest impact on clinical practice. It would also involve a diagnostic test that is currently not sensitive or specific enough for the disease as it would suggest that there is a clinical gap to fill by the CDS. A large variety in practice patterns for the work-up of the disease in question would make the creation of a CDS useful as it would standardize patient care. Moreover, if physicians currently feel like they are over-ordering tests to rule out the disease and the CDS can reduce test ordering, it would be particularly useful and likely to be rapidly adopted into clinical practice. Furthermore, a CDS can be highly favourable if it can fill the gap in diagnostic accuracy provided that the current clinical accuracy for the work-up of a disease is low or could be improved.

In terms of rigorous methodological standards, a CDS is particularly well constructed if the outcome that it is designed to predict is clinically important and well defined. Similarly, predictor variables should be well defined. The outcomes and predictor variables should ideally be collected prospectively and independently without knowledge of the other to avoid observation bias. This is especially important when the outcome is subjective as a physician tasked with determining whether a patient had a positive outcome could be influenced by having knowledge of predictors in that patient. Also, the reliability of the predictor variables should be high, meaning that the same findings will be noted by multiple physicians. The types of patients that the CDS was based on (inclusion and exclusion criteria, clinical and demographic setting and study setting) should be well defined so as to ensure a reproducibility of the results in new and different patient groups. In order for the CDS to make robust predictions, the sample size of the study should be large enough to have a minimum number of 10 events per predictor variable (EPV) in the

multivariable logistic regression (LR) analysis, although there has been some new literature on the topic suggesting that the EPV can be lower than 10 without affecting modeling. [49] The CDS should be derived by LR using variables selected a priori based on clinical sensibility and not univariate analysis. Older models were derived by sequential analysis in which potential variables were evaluated in isolation for their association with the outcome (univariate analysis). The variables with the strongest association to the outcome were then used in multivariable LR analysis. Sequential analysis is however limited as the univariate analysis performed initially can prematurely exclude certain variables which may eventually be found to have a strong association with the outcome when taking into account the effect of other variables during multivariable LR analysis. In addition, the ideal CDS would have a high sensibility meaning that it is clinically reasonable, easy to use and provides a specific course of action. Lastly, the CDS should exhibit good performance characteristics which can be assessed by multiple measures (e.g., sensitivity, specificity, predictive values, likelihood ratios, area under curve (AUC), calibration). However, in emergency medicine the focus is on sensitivity, negative predictive value and negative likelihood ratio as many of the diseases that are encountered in the ED carry morbidity and potential mortality, and as such false negatives can carry significant burden.

1.3.3 Chest Pain Clinical Decision Scores

As clinical gestalt has been shown to be insufficient for the ruling in or ruling out of ACS in ED patients, rules have been developed to aid the ED physician in the work-up of undifferentiated chest pain patients with suspected ACS. [50] The two most commonly used scores are the 2-hour accelerated diagnostic protocol (ADAPT) score and the history ECG age risk factors troponin (HEART) score.

1.3.4 ADAPT Score

The ADAPT score combines the Thrombolysis in Myocardial Infarction (TIMI) score (age ≥65, ≥3 CAD risk factors, known CAD, aspirin use in the last 7 days, severe angina symptoms) with ECG ischemic changes and abnormal conventional troponin assay results at 0- and 2- hour to evaluate risk of ACS in undifferentiated chest pain patients. [11] According to the score, patients who have a TIMI score of 0, absence of ECG ischemic changes and normal troponin results can safely be discharged from the ED. The initial prospective derivation trial on 1,975 patients, showed that this CDS had a sensitivity of 99.7% for MACE, measured at 30 days following ED presentation, and that it could correctly classify upwards of 20% of chest pain patients as low risk allowing for their safe discharge from the ED without further testing. [11] However, the study was derived in a Pacific population (one site in Australia and another in New Zealand) and as such its generalizability in patient populations outside of the Pacific area was questioned.

A 2015 study enrolling patients ≥30 years of age from 5 United States of America tertiary care centre EDs applied the ADAPT score to its North American population and found a much lower sensitivity for MACE (83.9%). [51] The authors deduced that the elevated sensitivity in the original study may have been because the derivation study included patients who were diagnosed with an NSTEMI based on the first troponin result while in their North American study, patients with an initially elevated troponin were not included in the study population. It can be argued that a CDS for an undifferentiated chest pain patient with a sufficiently elevated troponin marker is not necessary as the troponin marker alone would suggest an MI.

1.3.5 HEART Score

The HEART score was initially derived in 2008 in a study enrolling 120 admitted chest pain patients at a small community hospital in the Netherlands. [52] The study followed patients

for up to 6 weeks following their index ED visit and reported on 5 predictors (history, ECG, age, CAD risk factors and contemporary troponin results) that were found to be associated with MACE.

The score was then validated in a multi-centre study at 4 hospitals in the Netherlands in 2010 and quickly became the CDS most commonly used for undifferentiated chest pain patients at risk of ACS. [12] It included chest pain patients admitted to the ED including those with STEMI. History for each of the 880 patients enrolled in the study group of the validation study was classified by 2 or more investigators as being nonspecific, moderately suspicious, or highly suspicious for ACS. ECGs were rated by 2 cardiologists as either being normal, having repolarization abnormalities without significant ST-segment depression/elevation or as having significant ST-segment depression/elevation in the absence of a bundle branch block or left ventricular hypertrophy or digoxin use. Age was classified as less than 45 years, 45-65 or greater than 65 years. The presence of known CAD and classic risk factors for CAD such as hypertension, diabetes, active smoking, hypercholesterolemia, premature family history of CAD was noted. The total number of risk factors was used to categorize patients as having: no risk factors, 1-2 risk factors or $\geq$3 risk factors (patients with known CAD would belong to this category regardless of the number of risk factors as they were already known to have the disease). Lastly, the initial contemporary troponin levels were categorized as either normal if they were below the positivity threshold of the test, somewhat abnormal if they were between 1 and 3 times the positivity threshold for positivity or definitely abnormal if they were 3 times higher than the positivity threshold. The researchers then attributed 0-2 points for each of the following categories: history of the chest pain episode, ECG characteristics, age of the patient, risk factors and contemporary troponin results. A total score of 0-3 was considered low risk for MACE at 6 weeks (risk of 0.9-1.7%) while a score of 7 or more was considered high risk for MACE at 6 weeks (risk of 50-65%).

HEART Score [53]	
History	Highly suspicious 2 Moderately suspicious 1 Slightly or non-suspicious 0
ECG	Significant ST-depression 2 Nonspecific repolarization disturbance 1 Normal 0
Age	Age ≥65 years 2 >45–<65 years 1 ≤45 years 0
Risk Factors	≥3 risk factors, or history of atherosclerotic disease 2 1 or 2 risk factors 1 No risk factors 0
Troponin	Troponin ≥3× normal limit 2 >1–<3× normal limit 1 ≤Normal limit 0
Total Score	/10

The HEART score's main advantages over the ADAPT score is that it incorporates chest pain history and only requires the value of a single troponin in its calculation. On its own, the historical component in the validation study of the HEART score was found to have a negative predictive value of 95.8% for MACE in patients in whom the history was rated as nonspecific. Attesting to its performance in the clinical setting, the HEART pathway which uses this score to identify low risk chest pain patients has shown an overall reduction in cardiac testing, length of stay in the ED and an increase in early discharges. [54]

In a meta-analysis on 44,202 patients, the HEART score was found to be excellent at predicting MACE, and especially excelled at predicting MI and death. [55] However, there is new literature suggesting against its widespread use as a single tool to predict disposition as researchers reviewing charts in a prospective study were found to only have moderate agreement with the HEART scores calculated by clinicians [56]. This may be because the historical element is quite subjective in the score as all other variables within it are well described and delineated. The HEART score is also limited as it requires the value of a troponin and has only been validated with contemporary troponins which are being phased out of the EDs in favour of high-sensitivity

troponins. [53] Lastly, as each variable in the score is capped at 2 points and low scores include patients with a total score of 3 or less, it is possible that patients with isolated suspicious chest pain histories or significant ST depressions or elevated troponin could be categorized as low risk by novice medical providers/users of the score.

1.3.6 Additional Acute Coronary Syndromes Clinical Decision Scores

GRACE and TIMI are additional CDS that have been developed for ACS. They are often used inappropriately in undifferentiated chest pain patients. The GRACE score for example was developed to estimate in-hospital death and six-month risk of death or MI in patients with ACS. [57] The GRACE score is therefore not designed to predict MI in ED patients presenting with chest pain who do not already have an established ACS diagnosis. The TIMI score meanwhile was developed to prognosticate patients with an established diagnosis of UA/NSTEMI predicting death and ischemic event rates to ultimately guide management in this specific patient population. [58] Therefore, the GRACE and TIMI scores, do not help the ED physician predict MI or death in ED patients with undifferentiated chest pain. Moreover, the HEART score has been shown to outperform both of them with a greater AUC and a lower missed MACE rate when studied on the same patient population. [59]

1.4 LOGISTIC REGRESSION

Clinical decision scores have classically been derived using multivariable logistic regression (LR) models as they are used to predict a binary outcome: presence or absence of a disease. Multivariable LR is designed to adjust the effects of one variable while taking into account the effects of others and as such expresses the importance of each variable in the model using adjusted odds ratios, which are a function of the parameter estimates for each variable. [60] By

converting the individual parameter estimates into whole integers, a score can be tallied up reflecting an individual's risk of having the index disease.

LR models were previously developed by first performing univariate analysis for each variable collected to determine if there was an association between the predictor variable and the outcome. The variables that are found to be significant during univariate analysis or those with the highest ORs were selected for multivariable regression in which the effect of the variables is adjusted taking into the effects of other variables. Today, development of LR models usually follows a different approach. Instead, all variables of interest are now entered in a multivariable regression model and variables are either added or removed in a stepwise fashion (forward selection or backward elimination respectively). The forward selection method of regression adds variables in an order by which the ones with the strongest association to the outcome are added first and the ones with the weakest association are added last. Backward elimination regression meanwhile creates models by initially including all variables of interest in the model and then takes out the ones with the lowest association to the outcome. Commonly available software such as *Statistical Analysis System (SAS)*, *Statistical Package for the Social Sciences (SPSS)* or *Stata*, can run on a standard computer and can assist with this procedure which would otherwise be too difficult to perform with a large number of variables.

LR is not without its pitfalls. First, the variables inputted into the model need to be carefully considered so as to avoid relationships that are not clinically or scientifically plausible. [61] Moreover, variables that are expected to be highly correlated with one another should not be used concurrently. Even if variables are appropriately chosen, additional issues can arise with the conversion of continuous variables into categorical variables as there is loss of information and the precision of the model can be affected. [62] In addition, it has been suggested that the number of variables in multivariable regression analysis should be restricted to achieve an event per variable (EPV) of around 10 as models with low EPVs can lead to biased regression coefficients

although that is now debated with recent literature suggesting that the threshold can be lower. [63] A large sample size is also required to run the Hosmer-Lemeshow Goodness of Fit Test with enough power to detect outliers from the model. [64]

1.5 MACHINE LEARNING

Although LR models are useful in the creation of clinical decision scores, they are restricted by the biases of the humans constructing them as variables inputted into these are often based on clinical concepts that are well documented or generally thought to increase the likelihood of a certain diagnosis. A promising solution to identifying and incorporating novel variables is with the use of artificial intelligence (AI).

Machine learning (ML), a form of artificial intelligence, is characterized by its ability to learn over time, without being programmed, about patterns and relationships as it is presented with new data. [65] ML can be further subdivided into supervised (data sets are labelled and there is an identified output to predict), unsupervised (data is unlabelled and there is not an identified output to predict) or deep learning methods (uses multiple layers of nodes to associate variables together similar to a traditional biological neuron system). [66] Although deep learning methods seem to hold the most promise for creating predictive systems, they require a much larger amount of information in order to properly learn when compared with the other forms of ML and require a greater amount of computation power making them more expensive to train. As such, supervised ML techniques have largely been the ones employed in the medical field to predict outcomes. [67] Random Forest (RF) is a type of supervised ML and works by creating multiple uncorrelated classification and regression trees by randomly picking out data from a dataset for each tree to use. The model then evaluates the trees it has created by using other random data from the data set. [68]

RF has some advantages over LR. It generally has a high accuracy, is less likely to overfit, can better accommodate outliers and is not affected by multicollinearity. [69, 70] It can also process a greater number of variables and data sets. [71] ML also has some advantages over clinical decision scores. For example, ML has the unique ability to consistently improve its performance by analyzing new data and incorporating new variables into the algorithm as it learns. Another advantage of ML is the speed at which it performs its tasks, outperforming physicians. For example, in an algorithm designed to aid radiologists to identify intra-cranial hemorrhage on CT imaging in the outpatient setting, it reduced the time to diagnosis of new intra-cranial hemorrhage by 96% [72]. However, it does also have some limitations.

First, the creation of multiple decision trees which is inherent to this statistical method requires a large sample size. In fact, as many as 200 EPVs are required for adequate modelling. [73] The stability of the trees created is also determined by their depth or the number of variables they contain. Also, the clinical importance of each predictor in the model is more difficult to interpret than the odds ratio (OR) obtained via LR which gives the clinician a good estimate of the increase in odds of having an outcome if a predictor variable is present. [74]

1.6 MACHINE LEARNING APPLICATIONS FOR EMERGENCY MEDICINE

In the ED setting, ML was initially developed for image recognition helping to identify lung pathology such as pneumonia and fractures with sensitivities ranging from 85-95%. [75] Recently, ML use in the ED has been studied to improve the triage process and to predict specific diseases. In a 2019 study comparing a deep-neural network, a RF model and a LR model obtained using the Emergent Severity Index Score (similar to the Canadian Triage and Acuity Scale tool used for triage of ED patients), the ML models outperformed the Emergent Severity Index LR model in determining which patients would require critical care or hospitalization. [76] The

superiority of ML over clinical performance, has also been shown in a 2018 study which used 211 variables to retrospectively develop urinary tract infection diagnosis algorithms found to be more sensitive and specific for this diagnosis than clinical impression. [77]

The applications of ML have recently expanded to clinical decision tools. In a multi-centre study, a quick sepsis-related organ failure assessment score (qSOFA)-based ML model outperformed the traditional qSOFA score in predicting three day mortality in adult patients with suspected infection. [78] The performance of ML has also been compared with that of the Canadian Syncope Risk Score and was shown to be just as performant at identifying syncope patients at high risk of 30-day adverse events with the added advantage of using less variables than the original risk tool. [79]

However, not all studies published on ML rule in its favour as compared with tradition statistical techniques. A systematic review comparing ML to LR failed to show a performance benefit for ML in clinical prediction models. [80] The authors of this review published in 2019 included 71 original clinical medicine studies, most of which were in the oncology and cardiovascular fields, published over a 1.5 year time frame comparing clinical prediction models developed using LR with at least a single ML method such as trees, random forest or artificial neural networks for binary outcomes. As many of the included studies compared more than one ML method with LR, the authors identified 282 comparisons between LR and ML models. The authors then categorized the studies by determining whether they were at low or high risk of bias when they compared statistical techniques. Studies were considered to be at low risk of bias if they had a clear validation of model performance and if there was no difference between the LR and ML algorithms in: use of data-driven variable selection, handling of continuous variables, considered predictors or methods for class imbalance. The study determined that in the studies that they considered to be at low risk of bias, representing 145 of the 282 comparisons (51%), the performance of the LR models was similar to that of the ML models. It also concluded that aside

from trees which had the worst performance out of all ML methods identified, all other ML algorithms were similar in performance.

1.7 MACHINE LEARNING AND ACUTE CORONARY SYNDROMES

ML was first used to improved ECG detection of ACS. Applying a ML algorithm to ECG physician interpretation yielded a 37% increased sensitivity when compared with the interpretation of the ECG by an experienced physician alone. [81] A different study used demographics (age and sex) alongside troponin and performed better at identifying MIs than the commonly used 0/3-hour troponin pathway. [82]

In 2019, an algorithm called MI^3 was developed using prospectively collected data from multiple centres in various countries and was shown to outperform the European Society of Cardiology 0/3-hour pathway with an MI sensitivity of 97.8% and a specificity of 96.7%. [83] The MI^3 model did however use paired troponin values and included both the magnitude and rate of change in troponin concentrations to arrive at its AUC of 0.96 for MI on presentation to the hospital and its AUC of 0.96 for MI within 30 days of hospital discharge.

Using troponin in ML algorithms has been shown to increase performance. For example, in a 2021 study, a deep learning model was developed to diagnose NSTEMIs on ECGs using data from ECGs alone and data from ECGs alongside the value of a single troponin. [84] The inclusion of troponin in the model increased the AUC from 0.88 to 0.98, significantly improving the performance of the algorithm. An additional study, comparing a ML algorithm with clinical decision scores, developed an algorithm using troponin amongst a variety of predictors for MI on ED visit and explicitly only included patients with a troponin drawn as the authors desired to only include a high risk population in the study. [85] The algorithm developed by this group was shown to outperform both the TIMI and GRACE scores.

Despite these encouraging results, not all studies on ML developed algorithms and MI diagnosis have reported positive results. A study on 2.27 million patients using retrospective data from electronic health records aimed to create an algorithm using deep neural networks to predict MI at 6 months following the last visit on record. [86] The authors developed a model with an AUC of 0.84 but ultimately concluded that the benefit of their model was only moderate when compared to LR that used known risk factors of MI as calibration of the models was poor and there was overfitting of the models due to the low frequency of the outcomes.

1.8 RATIONALE FOR THE STUDY

ACS carries significant morbidity and mortality. Existing CDS for chest pain patients such as the HEART score rely on troponin results delaying the diagnosis and treatment of ACS. In the era of advanced computational power using novel AI techniques in lieu of traditional statistical techniques, we seek to determine if ML can outperform LR in identifying patients at highest risk of MACE. We also seek to determine if ML can outperform LR in identifying patients who are unlikely to have an abnormal troponin. A prognostic CDS predicting which patients are at highest risk of MACE, without the use of troponin, could be used to expedite urgent cardiology evaluation of certain patients. Furthermore, the creation of a diagnostic CDS for ultra-low risk chest pain patients could be used to identify patients that may be safely discharged from the ED without having to draw a troponin.

CHAPTER 2: OBJECTIVES AND HYPOTHESIS

2.1 OBJECTIVES

Current CDS for the work-up of undifferentiated chest pain do not incorporate well-defined chest pain characteristics that have been shown in literature to be predictive of ACS and rely on troponin results which can be delayed, and in turn, postpone urgent cardiology evaluation of patients with MACE. There are also no published CDS that can predict which patients will have an abnormal troponin and so many chest pain patients undergo unnecessary troponin testing. As such there are clear gaps in the CDS that are currently available for ED physicians who assess patients with chest pain.

AI techniques have recently shown promising results in predicting disease in the ED population for a series of diseases including cardiovascular emergencies. They may further improve on CDS. We seek to explore the performance of ML comparing it with commonly used LR in predicting MACE and abnormal troponin results in chest pain patients.

The specific objectives are as following:

(i) To determine the 6-week outcomes of ED undifferentiated chest pain patients;

(ii) To develop and internally validate a MACE predictive model using LR that does not use troponin but incorporates specific chest pain characteristic to predict which undifferentiated chest pain patients are at highest risk of MACE on their index ED visit or within 6 weeks of their index ED visit;

(iii) To develop and internally validate an abnormal troponin predictive model using LR that can predict the likelihood of an abnormal troponin before it is drawn in undifferentiated chest pain patients;

(iv) To compare the MACE and abnormal troponin LR models with ML models created by a researcher blinded to the LR model; and

(v) To develop a novel CDS that incorporates specific chest pain characteristics without relying on troponin and to build a CDS to predict which patients are likely to have an abnormal troponin.

2.2 HYPOTHESIS

We hypothesize that ML will outperform LR in the creation of predictive algorithms for MACE and abnormal troponin. We however expect that LR will still be able to yield useful CDS.

CHAPTER 3: METHODS

3.1 STUDY DESIGN AND SETTING

We conceived and implemented a retrospective observational cohort study which included chest pain patients who presented to the ED of two adult hospitals in Ottawa, ON (Civic Hospital and Ottawa General Hospital which are part of The Ottawa Hospital institution) between November 27th 2019 and January 8th 2020.

3.2 SELECTION OF PARTICIPANTS

Consecutive adults presenting to the ED of the Civic or Ottawa General Hospitals with atraumatic chest pain during the study period were included.

3.2.1 Inclusion Criteria

Patients were included if they met all of the following inclusion criteria:

(i) ≥ 18 years of age

(ii) had either a high sensitivity troponin drawn or an ECG done

(iii) had non-traumatic chest pain as their primary complaint

3.2.2 Exclusion Criteria

Patients were excluded if they met any of the following exclusion criteria:

(i) < 18 years of age

(ii) did not have a troponin drawn or ECG done

(iii) had traumatic chest pain

(iv) diagnosed STEMI prior to or on immediate arrival to the ED

(v) transferred from another hospital

(vi) left unseen by the physician

(vii) had a stress test or angiogram within 1 month of the ED visit

(vii) had a cardiac procedure (catheterization or ablation)/surgery, within 1 month of the ED visit

(viii) resided outside of the Ottawa area

3.3 DATA COLLECTION & SAMPLE SIZE

Data on patient demographics, initial ED course, past medical history, medications, history of presenting illness, vital signs, ECG characteristics, troponin values, and final ED diagnosis during the index ED visit were collected independently by four data abstractors. We also collected the results of all pertinent investigations (including nuclear tests and coronary angiogram) performed during the index ED visit hospitalization or during follow-up in relation to the index ED visit for chest pain. We collected the final diagnosis for the presenting complaint of chest pain, at the end of the follow-up period by reviewing the patient's electronic health records. We performed quality checks of collected data by reviewing charts alongside the corresponding completed data collection forms at random throughout the data collection process. We recorded the collected data using a password protected digital data collection form (Appendix 1).

We aimed to include at least 40 patients with MACE as part of our study allowing us to derive a MACE LR model using at least 10 variables based on recent literature suggesting that the minimum EPV is lower than 10. [87] Based on a 4% prevalence of MI in chest pain patients presenting to the ED, we estimated that we would require a minimum of 1,000 patients for analysis while having an EPV≥4. [88]

We expected abnormal troponins to be present in about 12% or 1 out of 8 patients in our study population based on a 2019 prospective cohort study which enrolled consecutive patients who had a troponin drawn as part of their ED visit. [89] As we aimed to create an abnormal troponin LR model using at least 14 variables and once again aimed to have an EPV≥4, we estimated that we would require at least 470 patients for analysis.

3.4 PREDICTOR VARIABLES

3.4.1 Demographics and Initial Emergency Department Course

Demographics information and initial ED course included the patient's age during the visit, their sex, whether the patients arrived by ambulance or on their own to the ED and whether they were placed on a cardiac monitor prior to being assessed by the ED physician or immediately afterwards. Age and sex were chosen as they are commonly cited non-modifiable ACS risk factors. Arrival by ambulance or monitored in the ED were chosen as variables of interest as they can act as objective signs of disease severity and are readily available in patients' medical records. Monitored in the ED has the additional advantage of being a reflection of nurse or physician clinical gestalt regarding a patient's overall state as monitored beds are reserved for the sickest patients.

3.4.2 Past Medical History

Past medical history information recorded included whether the patient was already known for coronary artery disease (CAD) or for angina and whether they had known risk factors of ACS: family history of CAD, prior/active smoker, hypertension, diabetes, hypercholesterolemia, and obesity. We also retained information on other types of vascular diseases which are known to co-

exist with CAD: presence of prior transient ischemic attack (TIA), prior cerebrovascular accident (CVA) or known peripheral vascular disease (PVD). We also collected information on other types of cardiac history that are sometimes associated with CAD or that can also occur in isolation: congestive heart failure, ICD/pacemaker, atrial arrhythmias (atrial fibrillation or flutter), ventricular arrhythmia (ventricular tachycardia or fibrillation) and cardiac arrest. Lastly, we recorded non-cardiac comorbidities: chronic obstructive pulmonary disorder (COPD), renal failure, and pulmonary embolism.

3.4.3 Medication History

We kept track of the medications that patients were taking in our study as they may serve as surrogate markers for disease in patients who do not recall what conditions they have or in instances of incomplete documentation in a chart. Some medications such as aspirin and statins have also been shown to lower the risk of ACS. [90] More specifically, we recorded whether patients were on antiplatelet medications (aspirin or clopidogrel or ticagrelor) which are commonly prescribed to patients that are either at risk or known for vascular disease, whether they took an anticoagulant (warfarin, rivaroxaban, apixaban, dabigatran) and whether they took commonly prescribed medications for hypertension or cardiac diseases (congestive heart failure, arrhythmias, etc.) such as beta blockers, calcium channel blockers, ace inhibitors, or angiotensin receptor blockers. Moreover, we recorded whether patients were taking nitroglycerin or other nitrates. This class of medication is commonly used in patients with angina to palliate symptoms. Finally, we documented whether patients were on a cholesterol lowering medication (statins or fibrates).

3.4.4 History of Presenting Illness

History of presenting illness (HPI) was obtained from the ED physician's note. Based on literature, symptom characteristics increasing the likelihood of an MI such as crushing chest pain, exertional symptoms, radiating chest pain, relieved by nitroglycerin, middle or left sided chest pain, associated symptoms of shortness of breath/diaphoresis/gastrointestinal symptoms were recorded. [52, 91] Characteristics of chest pain more likely related to other diseases such as tearing pain (aortic dissection), pleuritic pain (pulmonary embolism), positional pain (pericarditis) or associated symptoms such as fever (pneumonia) were also recorded. As ED notes are brief, it was assumed that the absence of a symptom characteristic in the chart meant that the patient did not exhibit it. All HPI variables were dichotomized into either the presence of absence of the respective characteristic.

3.4.5 Triage Vital Signs

The first recorded hospital vital signs were obtained from the triage note. If the vital signs were not present in the triage note, the first vital signs recorded in the patient's chart were included. Vital signs included heart rate in beats per minute (bpm), respiratory rate in breaths per minute, systolic and diastolic blood pressure in mmHg, temperature in degrees Celsius and oxygen saturation as a percentage including whether patients were on supplemental oxygen when the oxygen saturation was taken. All continuous variables were dichotomized based on what are clinically significant abnormal vital signs. Heart rates below 60 or above 100 bpm were abnormal and classified as such. Similarly, a respiratory rate below 12 or above 20 breaths per minute was also considered to be abnormal. Blood pressure cut-offs for an abnormal systolic blood pressure were <90 and >160 mmHg while those for an abnormal diastolic blood pressure were <60 and

>100 mmHg. A temperature <35°C or >38 °C was abnormal. Lastly, an oxygen saturation <95% was abnormal.

3.4.6 Electrocardiogram Characteristics

The initial 12-lead ECG performed on patients was interpreted by a single researcher who is also an ED physician (CT). Measurements of the heart rate, QRS axis and intervals (PR, QRS, QTc) as calculated by the ECG machine were recorded. The underlying rhythm was categorized as either sinus or non-sinus. In cases in which the rhythm was noted to be non-sinus, we reviewed the patient's prior ECG to confirm if it was pre-existing or new. In instances in which the patient did not have a prior ECG, the rhythm was noted as "not known to be old". As ventricular tachycardia and fibrillation are often caused by ACS, we tracked these rhythms as a subcategory of non-sinus rhythm. [92] We also recorded the presence of not known to be old left and right bundle branch blocks (LBBB and RBBB respectively) as these have also been shown to be caused by cardiac infarction affecting the conduction system of the heart. [93, 94] Commonly encountered, not known to be old, ischemia changes such as ST segment depressions and T wave changes (territorial flattening or inversions) and infarction changes consisting of pathological q waves (> 40 ms wide, > 2 mm deep, > 25% of depth of QRS complex, in leads V1-V3) were recorded.

The final interpretation of the ECG was rendered as:

(i) Normal

(ii) Nonspecific ST-T wave changes

(iii) Abnormal but not diagnostic of ischemia

(iv) Infarction or ischemia known to be old

(v) Infarction of ischemia not known to be old

(vi) Uninterpretable

Normal ECGs included those that were in sinus rhythm or were paced by an implantable pacemaker but did not have any new change compared to the patient's baseline. ECGs reported as nonspecific ST-T wave changes contained ST or T wave changes that were not territorial (contiguous leads) or that were not pronounced enough to be classified as ischemic. ECGs categorized as "abnormal but not diagnostic of ischemia" contained old bundle branch blocks or new RBBB or non-sinus rhythms (except known to be old paced rhythm). ECGs containing pathological q waves or ischemic ST or T wave changes were either interpreted as "infarction or ischemia known to be old" if the changes were present on a prior ECG or "infarction or ischemia not known to be old" if the changes were not present on a prior ECG or if a prior ECG was not available. ECGs with not know to be old LBBB were categorized as "infarction of ischemia not known to be old" as LBBBs are more often caused by ischemia than RBBB. CT also interpreted the second ECG done in the ED for patients that had more than one ECG and noted whether there was evidence of new ischemic changes.

3.4.7 Troponin

The value of the first hs-Trop that was resulted was collected and classified as either normal (initial hsTnI≤14ng/L) or abnormal (initial hsTnI>14ng/L). The cut-offs chosen were as per the manufacturer's recommendations for the hs-Trop assay at the study sites. If a patient had subsequent high-sensitivity troponins that were abnormal before a disposition decision was taken by the ED physician, we recorded it as "any high sensitivity-troponin >14ng/L" regardless of which troponin blood tests (first, second, third or fourth of the visit) resulted above the 14ng/L threshold.

3.4.8 Predictor Variable Selection

Mandatory predictor variables were selected a priori before collecting data on patients. We considered variables to be mandatory based on the expected strength of the association between the variable and outcome of interest. Depending on the total number of MACE and patients with abnormal troponin values that we recorded in the study population, additional variables were included in the derivation of the model (optional variables) while aiming to have an EPV of at least 4. More variables than required for derivation of the LR models were collected as we did not know the number of outcomes ahead of time and aimed to include as many variables as possible when deriving the models. Furthermore, ML can handle a greater number of variables and can identify variables of interest that were not selected in the LR models.

MACE LR Model Mandatory Variables (10)

RISK FACTORS
Age>65, active smoker, family history of coronary artery disease, vasculopathy (diseases affecting vascular structures), metabolic disease (chronic diseases which increase the risk of MI)

CLINICAL GESTALT
Monitored in the ED

SYMPTOM CHARACTERISTICS
Exertional or relieved by rest, relieved by nitroglycerin, radiates to jaw or arm

ECG
Final ECG interpretation suggestive of infarction or ischemia not known to be old

Abnormal Troponin LR Model Mandatory Variables (14)

RISK FACTORS
Age>60, active smoker, male sex, family history of coronary artery disease, metabolic disease

NON-ACS CAUSES of ELEVATED TROPONIN
Congestive heart failure, renal failure, atrial fibrillation/flutter, pulmonary embolism

CLINICAL GESTALT
Monitored in the ED

SYMPTOM CHARACTERISTICS
Exertional or relieved by rest, relieved by nitroglycerin, radiates to jaw or arm

ECG
Final ECG interpretation suggestive of infarction or ischemia not known to be old

3.5 OUTCOME MEASURES

A composite outcome of MACE was used. The definition of MACE found in literature varies but includes at least three points: acute MI, ischemic stroke and cardiovascular death. [41] In addition to these, we also included revascularization (PCI or CABG) as did the prospective validation of the HEART Score. [53] Angiographies without revascularization by a balloon or stent were not included as part of our composite outcome as up to 60% of angiographies performed do not show a lesion that is hemodynamically significant. [95] Unstable angina (UA) meanwhile was included as part of the composite outcome but the suspicion of significant coronary stenosis had to be confirmed by either a positive stress test (exercise or nuclear) or angiography. Lastly, ventricular arrhythmia (sustained ventricular tachycardia or fibrillation) secondary to a blocked coronary and cardiac arrest were also included. Our seven-point MACE composite outcome included acute MI, ischemic stroke, cardiovascular death, revascularization, UA, ventricular arrhythmia and cardiac arrest.

The occurrence of MACE on the index ED visit or within 6 weeks of the visit was considered to be a positive outcome. We chose the primary outcome that the patient suffered in order of severity as follows from the most severe to the least: death (regardless of whether it was due to a cardiac or unknown cause), cardiac arrest, ventricular arrhythmia, revascularization procedure (PCI or CABG), acute MI (STEMI or NSTEMI), UA, ischemic stroke. In addition, we also reported on any MACE, that is included in our seven-point composite outcome, that a patient suffered from during the study period.

Follow-up of patients was done by systematically searching our local hospital electronic medical records (EMR) database for any visits or cardiac investigations including revascularization procedures up to 6 weeks following the index ED visit. The Civic Hospital and

Ottawa General Hospital use the same EMR and as such as long as a patient returned to one of the sites belonging to the network of The Ottawa Hospital, visit information would be available. Furthermore, the Heart Institute which is affiliated with The Ottawa Hospital, also uses the same EMR and is the only facility in the region with capabilities for cardiovascular interventions such as angiography, PCI or CABG. As such, any revascularization procedure taking place in the city during our study period would have been recorded and accessible to our team.

3.6 DATA ANALYSIS

Continuous variables such as age were reported by means, medians, standard deviations and ranges where appropriate. Categorical or dichotomous variables meanwhile were described using frequencies and percentages. Data analysis was performed using SAS Version 9.4.

3.7 MISSINGNESS OF DATA

We expected data for demographics, initial ED course and final ECG interpretation to be complete. Demographics and initial ED course data are readily available for any patient that is seen in the ED as they're collected by registration before the patient is seen by a physician or in the case of the "monitored in ED" variable, is recorded systematically by nursing. ECG interpretation was performed for all patients who had an ECG done in the ED and was not expected to be missing unless a patient did not have an ECG. We also assumed that patients who did not have an ECG during their visit were likely considered to be at low risk of ACS or other cardiovascular disease including arrythmia and would have likely had a normal ECG. This assumption is supported by research on the Canadian Syncope Risk Score which showed that

patients who did not have an ECG or troponin as part of their work-up for syncope were indeed low risk. [96]

The value of variables with missing data from past medical history, medications or history of the presenting complaint were assumed to be absent as ED charting is succinct. Pertinent positive such as known ACS risk factors, medications taken, or worrisome chest pain characteristic are meanwhile almost always documented as they justify the work-up of ACS. For patients that were seen by a consultant or admitted, we reviewed consultant notes to confirm the presence or absence of past medical history, medication and history of presenting complaint variables.

Missing triage vital sign data can also be assumed to be normal as patients who are otherwise well sometimes don't have vital signs done on their visit. In the event that vital signs were missing on the initial triage note, we recorded the first vital signs that were obtained in the ED which can sometimes happen when patients are immediately brought to a room for assessment. We chose to exclude any vital sign that was missing for more 5% of the patients included in our study when building our LR model. The cut-off of 5% was chosen based on an article by Schafer, on the indications and process of multiple imputation, which suggested that a missing rate of ≤5% is likely without consequence. [97] We did not perform listwise deletion or multiple imputation for missing data in our study, as we expected the missing data to be missing not at random (MNAR). Both of those techniques require data to be missing completely at random (MCAR). For the ML model meanwhile, which retained all vital signs in their original continuous variable form, we performed mode imputation for missing vital signs. This was deemed to be an appropriate estimate of the true vitals of the patients that did not have them recorded as vital signs have a limited range and tend to cluster due to physiology.

3.8 LOGISTIC REGRESSION

Two different parsimonious multivariable LR models were built using backward elimination with a requirement of $p < 0.05$ for any retained predictor variable. A summary of the 71 potential predictor variables that were collected is included in Appendix 2. The first model used MACE as an outcome and the second used an abnormal high sensitivity troponin (defined by our assay as a hsTnI >14) as an outcome.

Prior to multivariable regression analysis, a check for multicollinearity for the chosen variables was done in three different ways. First, a correlation matrix was built with Pearson correlation coefficients for the retained variables to determine if any variables had a high coefficient (defined as ≥ 0.8) [98]. Multicollinearity was then checked via the variance inflation factor and tolerance. Predictor variables with tolerance values ≥ 0.1 and variance inflation values ≤ 10 ruled out the possibility of multicollinearity. Lastly, an eigensystem analysis of covariance was performed. Eigenvalues which were not close to 0 and did not have an elevated condition index were used as indicators that multicollinearity did not take place in the model.

When building models, we considered using as many of the predictor variable categories as possible while avoiding collinearity. We restricted the analysis to a minimum number of events per variable (EPV) of 4 as studies have shown that below this threshold, issues with overfitting appear. [49, 87, 99] As troponin is used in the universal definition of an MI and is thus not truly an independent variable when dealing with MACE, we did not include it in the MACE model as a predictor. [100]. We also chose to only include the ECG final diagnosis in the models despite reporting descriptive statistics on more specific ECG changes suggestive of ischemia such as ST, T- wave, q-wave or new left bundle branch block. These ECG changes were considered to be equivalent to each other and could be summarized by the final interpretation of the ECG which

was dichotomized as either the absence or presence of not known to be old ischemia. This allowed us to include a greater number of non-ECG related variables in the analysis.

AUC with 95% confidence intervals (CI) was used to determine the performance of the model. Hosmer and Lemeshow Goodness-of-Fit Tests were performed to determine the fit of the LR curve to the data of the study. A cut-off of <0.05 for the Pr > ChiSq was used as a threshold to suggest that the models were a poor fit. [101, 102] In addition, to assess fit, calibration curves were constructed. Moreover, receiver operator characteristic (ROC) curves were built for each model using the SAS statistical software.

Internal validation of the multivariable logistic regression models was performed by bootstrapping with replacement the original dataset 500 times. Model performance with 95% confidence intervals alongside optimism were reported.

3.9 MACHINE LEARNING

A separate researcher (LG) was instructed on the study design, data collected and key steps. They were recruited to help with the technical aspects of ML by using Python Version 3.7.6 software and were blinded to the LR models and CDS scores. They were provided with clean data adjusted for missing data, based on the assumption that missing data from dichotomous variables is likely normal. They were instructed to consider using all of the collected predictor variables (Appendix 2), as we sought to determine if ML can identify variables that were not included in the LR models. Categorical predictor variables in which a single category (presence or absence) occurred in more than 90% of patients were not included as predictors in order to limit the depth of the trees as the inclusion of those common predictors would not have improved the performance of the trees but would have made them more unstable. Unlike with the generation of the LR models, continuous variables were retained in their original form and were not converted into

categorical variables as we did not aim to create a clinician-friendly score using the ML models. In instances in which data was missing from a vital sign predictor variable, the mode was used for imputation.

Random forest (RF) ML models using predictors to provide an estimated probability of MACE and abnormal troponin were developed. The RF models, using 59 remaining predictors, were trained using an isotonic calibration method which has the advantage of correcting monotonic distortion between variables. Monotonic data refers to variables in which a change in the value of one variable causes another variable to change in only one direction (either a decrease or an increase).

Unlike the LR model, individual ECG characteristics were used rather than the final ECG interpretation. To prevent overfitting and to obtain optimal hyperparameters, a grid search with 5-fold cross validation was used. As ML techniques do not yield ORs or maximum likelihood estimates, the relative importance of the 59 predictors in each model was assessed using the impurity-based feature importance. Following this, separate "trimmed-down" RF models for both MACE and abnormal troponin as outcomes were trained using only the top 8 predictor variables with the highest impurity-based feature importance. The performance of the 2 ML models for MACE and the 2 ML models for abnormal troponin ("full model" using all 59 variables and "8-variable model" using only 8-variables) was determined using AUC with 95% CI. Internal validation of the models was done by bootstrapping with replacement the original data set 1000 times. ROC curves were made using a quantile strategy.

3.10 COMPARISON OF LOGISTIC REGRESSION AND MACHINE LEARNING MODELS

The performance of the models in predicting MACE, and that of the models predicting an abnormal troponin on the visit, was determined by their respective AUCs with 95% CI. Overlapping CIs were considered to represent a similar performance while non-overlapping CIs suggested superior performance of a model.

3.11 CLINICAL DECISION SCORES

The LR models were converted into CDS using the regression coefficients of the predictor variables in the derived model. The lowest maximum likelihood estimate was used to divide all other variable estimates in order to obtain an integer above 1 for each variable. Integers were then rounded to the nearest whole number attributing a score for each variable. Risk groups were created based on the percentage of MACE observed in each total score category and on the score of individual predictor variables which are know to be strongly suggestive of ACS such as an ECG suggestive of not known to be old ischemia or infarction. Cut-offs for the low risk group was obtained by using the prevalence of <1% MACE as an acceptable threshold based on the American College of Emergency Physicians clinical policy on an acceptable missed rate of adverse cardiac events of less than 1-2% [103]. The cut-offs for the high risk group was obtained by limiting the prevalence of MACE in the intermediate group to <10% based on the HEART score in which the moderate risk group has a risk of MACE of 12-16.6%.

A CDS was similarly obtained using the derived LR model for an abnormal troponin. Whole integers for each variable were obtained using the regression coefficients for the predictor variables in the derived model. Five risk-groups were created: ultra-low risk, low risk, medium risk, high risk and very high risk. The ultra-low risk cut off was obtained by determining at which

total score abnormal troponins started appearing in our population. The goal of the score was to determine which patients were likely to have a normal troponin and could be cleared from an ACS standpoint without one and as such we aimed to have the highest possible sensitivity in the ultra-low risk group. The very-high risk cut-off was obtained by determining at which level more than 90% of patients in the group could be expected to have an abnormal troponin.

3.12 ETHICS

Ottawa Health Science Network Research Ethics Board (OHSN-REB) approval was obtained prior to the collection of data and enrolment of patients. All collected data was anonymized using unique patient identifier numbers, stored in the Ottawa Hospital Research Institute (OHRI) cloud and password protected.

3.13 STANDARDS OF REPORTING

Standards of reporting were respected by following the *Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis* (TRIPOD) checklist (Appendix 3).

CHAPTER 4: RESULTS

4.1 PATIENT FLOW

A total of 1,538 patient charts corresponding to ED visits occurring between November 27th, 2019 and January 8th, 2020 were reviewed. After applying exclusion criteria, 524 patients were excluded leaving 1,014 patients enrolled (Figure 1). More than half of patients not included in the study were excluded because they either lived beyond the catchment area of The Ottawa Hospital (138/524 excluded patients) or because they did not have either an ECG or a high sensitivity troponin drawn as work-up for their chest pain on the visit (135/524 excluded patients).

4.2 PATIENT CHARACTERISTICS

4.2.1 Demographics and Initial Emergency Department Course

The average age of patients in the study was 55.7 years and 48.4% of patients were males (Table 1). Nearly one quarter of the patients (24.0%) arrived by ambulance and almost half (44.4%) were monitored in the ED.

4.2.2 Past Medical History

CAD was known to be present in 24.0% of patients while 28.5% of patients did not have any past medical history (Table 1). The most common CAD risk factors were hypertension (39.5%), hypercholesterolemia (29.9%) and active smoking (19.1%). Of the medications recorded, patients most often took cholesterol-lowering medications (30.2%). Just under a quarter of patients (22.3%) were taking aspirin as an anti-platelet medication. ACE inhibitors/angiotensin receptor blockers were the most common class of anti-hypertensive medication prescribed with 22.2% of patients taking this medication. The majority of patients (53.3%) did not take an anti-platelet, anti-

coagulant, beta blocker, calcium channel blocker, ace inhibitor/angiotensin receptor blocker or nitroglycerin.

4.2.3 Chest Pain Characteristics

In terms of chest pain characteristics, 22.7% of patients described their pain as crushing or pressure-like, 12.8% had exertional chest pain or pain relieved by rest, 24.0% experienced the pain radiating to the jaw or arm and most (59.1%) experienced chest pain that was on the left side or middle of the chest (Table 2). Few patients described their pain as pleuritic (16.7%), positional (12.7%) or tearing (0.5%).

The most commonly associated symptom was shortness of breath with 30.2% of all patients reporting it alongside their chest pain. Of the symptoms that typically accompany chest pain in patients with ACS, diaphoresis was the least commonly encountered (9.0%). Meanwhile, fever was overall the least commonly associated symptom reported by patients (2.7%).

4.2.4 Vital Signs

The most commonly encountered abnormal vital sign was a systolic blood pressure <90 or >160 mmHg (18.6%), followed closely by a heart rate <60 or >100 beats per minute (18.3%) (Table 3). Only 1.1% of patients were on supplemental oxygen however data pertaining to this variable was missing in 13.7% (139/1014) of patients.

4.2.5 Electrocardiogram Characteristics

Nearly all patients had at least an ECG (99.0%) (Table 4). Twenty-two patients (2.2%) were found to be in a non-sinus rhythm that was not known to be old. However, none of these

patients had a ventricular tachycardia or ventricular fibrillation on their initial ECG. Most patients had a normal ECG (65.8%) while 4.4% had changes suggestive of ischemia that was not known to be old. T wave changes not known to be old was present on 20 of the 26 ECGs with not known to be old ischemia final interpretations and represented the most commonly encountered ischemic change. Of the 191 patients with multiple ECGs on the index ED visit, 10 had new ischemic changes on their second ECG.

4.2.6 Troponin Results

A total of 965 patients (95.2%) had a least a single troponin drawn (Table 5). Of the patients with troponin drawn, 77.2% of all patients had an initial troponin ≤14ng/L while 22.8% had an initial high sensitivity troponin >14ng/L. An additional 6 patients with an initial normal troponin had a high sensitivity troponin >14ng/L on repeat troponin performed before ED disposition bringing the total number of patients with an abnormal high sensitivity troponin at anytime during the visit to 226 (23.4%).

4.3 OUTCOMES

70 patients had at least a single outcome either during the index ED visit or within 6 weeks of the ED visit (Table 6). Most patients experienced their MACE during the index ED visit (84.3%). Five patients (7.1%) experienced a MACE both on the index ED visit and during the 6-week follow-up. Only 6 patients (8.6%) had a MACE after the ED visit. Of the patients who suffered a MACE, more than three quarters (78.6%) had a revascularization procedure (stent or coronary artery bypass grafting) as their primary outcome. Four patients died of either a cardiovascular or unknown cause representing 0.4% of the entire study population.

In the 70 patients who suffered from at least a single MACE, there were a total of 133 MACE events: 43 stent revascularization procedures, 41 NSTEMIs, 20 unstable anginas, 15 CABG revascularization procedures, 4 ventricular arrhythmias, 3 cardiac arrests, 3 deaths of unknown causes, 3 STEMIs and 1 cardiac death (Table 7). Only 10 patients had a single MACE event. In addition to the patients with MACE, 17 patients (1.7%) had a potentially life-threatening diagnosis on index ED visit. (Table 8)

4.4 EXCLUSION OF VARIABLES DUE TO MISSING DATA

Data on temperature was missing for 10.6% of patients and as such we did not use it in the LR multivariable analysis for MACE or abnormal troponin. Also, although data on oxygen saturation was available in more than 90% of patients, the absence of a known concentration of breathable oxygen was missing in 13.7% of patients and it was decided that the variable would not accurately represent the oxygenation status of patients and would not be included in the MACE or abnormal troponin multivariable analysis.

4.5 MAJOR ADVERSE CARDIAC EVENTS MULTIVARIABLE ANALYSIS

Based on the 70 events that were reported in the study population, we capped the total number of variables in the MACE multivariable analysis to 14 for an EPV of 5.0 prior to the backward elimination of variables. A study suggesting the ideal number of EPVs in LR models reported that overfitting mainly occurs when the EPV is between the 2 and 4 range or when data sets using dichotomous variables have 30 or fewer events so we aimed to be above the 4 EPV threshold. [49] For this analysis we used data from all 1,014 patients included in the study. We selected the following variables for analysis:

1. Age >65
2. Monitored in the ED
3. Active smoker
4. Family history of CAD
5. Vasculopathy (at least 1 out of 4 of the following: coronary artery disease or transient ischemic attack or stroke or peripheral vascular disease)
6. Metabolic disease (at least 2 out of 3 of the following: hypertension or hypercholesterolemia or diabetes)
7. Crushing/pressure (optional variable)
8. Exertional or relieved by rest
9. Radiates to jaw or arm
10. Relieved by nitroglycerin
11. Heart rate <60 or >100 beats per minute (optional variable)
12. Systolic blood pressure <90 or >160 mmHg (optional variable)
13. Final ECG interpretation suggestive of infarction or ischemia not known to be old
14. QTc >500ms (optional variable)

We picked variables from each predictor category with the exception of medications as there was a medium interaction between vasculopathy and certain medications such as cholesterol-lowering medications. We felt that vasculopathy was a better predictor for MACE than medications and that we would have captured the presence of disease known to increase the odds of MACE by our metabolic disease variable which required the presence of at least 2 of the following: hypertension, hypercholesterolemia or diabetes. Creating the vasculopathy and metabolic disease variables was done in an effort to reduce the total number of variables while capturing the most information. We also reasoned that having multiple modifiable risk factors for CAD would increase the odds of MACE by a greater extent than by just having a single modifiable risk factor and would increase the chances that the variable would be retained in backward elimination. Other major risk factors of CAD such as smoking history and a family history of CAD

were included on their own in the analysis. We chose to include monitored in the ED as it reflects health care provider gestalt which is not captured by any other variable. Four chest pain features that are generally associated with ACS were included in the model separately as we sought to determine which specific historical features increased the odds of MACE. We chose to include vital signs impacted by cardiac function such as heart rate and blood pressure in the analysis as these are not in use in other chest pain CDS but can be affected by cardiac ischemia, infarction or arrhythmia. Lastly, two ECG features were included in the analysis. We chose to only include the final ECG interpretation rather than specific changes to limit the number of variables in the model. Meanwhile, a prolonged QTc was included in the model as it is known to increase the risk of arrhythmia but has not been a part of published CDS for chest pain patients.

Prior to the backward elimination and derivation of the model, we ensured that there was no significant collinearity between the selected variables. In the analysis of covariance by correlation matrix, all of the Pearson correlation coefficients were less than the >0.8 threshold which is used to identify strongly correlated variables (Appendix 4). More specifically, the highest Pearson correlation coefficient (0.42) obtained for monitored in the ED and vasculopathy (at least 1 out of 4 of the following: coronary artery disease or transient ischemic attack or stroke or peripheral vascular disease). All tolerance values for retained variables were ≥ 0.1 and variance inflation values were ≤ 10. (Appendix 5) Eigen values for retained variables were not close to 0 and did not have an elevated condition index (Appendix 6).

The derived MACE LR was composed of nine predictor variables (Table 9). The 3 variables with the highest ORs for MACE were QTc>500ms (OR 10.07, 95% CI: 3.38, 30.06), final ECG interpretation suggestive of infarction or ischemia not known to be old (OR 8.73, 95% CI: 3.94, 19.33) and monitored in the ED (OR 5.55, 95% CI: 2.53, 12.16). The variable with the lowest OR for MACE that was retained in the model was active smoker (OR 1.97, 95% CI: 1.08,

3.58). All retained variables in the model achieved statistical significance for their association with MACE (Table 10). The AUC for the model was 0.89 (95% CI: 0.86, 0.93) while the Hosmer and Lemeshow Goodness-of-Fit-Test was not statistically significant with a Pr > ChiSq = 0.25 and a chi-square of 7.89 suggesting that the model is not a poor fit for the data. A calibration plot for the derived model was constructed (Figure 2). A ROC curve for the derived MACE LR model was plotted (Figure 3).

Bootstrapping the original dataset with replacement 500 times yielded a similar performance of the model with AUC of 0.89 (95% CI: 0.87, 0.93) (Table 11). The optimism was 0.02 and the optimism-adjusted AUC was 0.87 (95% CI: 0.85, 0.91). Variables which are in the retained model appeared most frequently during bootstrapping and those with the highest ORs appeared most frequently (Table 12). Five out of the nine variables in the retained model appeared in more than 90% of the bootstraps.

4.6 ABNORMAL TROPONIN MULTIVARIABLE ANALYSIS

We capped the number of predictor variables in our abnormal troponin multivariable analysis to 22 based on the 226 patients who had an abnormal troponin for an EPV of 10.3. Although we could have included more variables, we did not feel that it was necessary and the addition of other variables such as vasculopathy resulted in collinearity with other variables that we had already included in the model. For this analysis, we included the 965 patients who had a troponin drawn. The following variables from each category of predictors, including medications, was chosen for analysis:

1. Age>60
2. Male sex
3. Arrival by ambulance (optional variable)

4. Monitored in the ED
5. Active smoker
6. Family history of CAD
7. Metabolic disease (hypertension and diabetes)
8. Congestive heart failure
9. Renal failure
10. Atrial fibrillation/flutter
11. Pulmonary embolism
12. Cholesterol-lowering medications (optional variable)
13. Crushing/pressure (optional variable)
14. Exertional or relieved by rest
15. Radiates to jaw
16. Relieved by nitroglycerin
17. Shortness of breath (optional variable)
18. Heart rate <60 or >100 beats per minute (optional variable)
19. Respiratory rate <12 or >20 breaths per minute (optional variable)
20. Systolic blood pressure <90 or >160 mmHg (optional variable)
21. Final ECG interpretation suggestive of infarction or ischemia not known to be old
22. QTc >500ms (optional variable)

A lower cut-off was chosen for the age variable than in the MACE regression analysis as some patients aged 61-65 had an abnormal troponin and we sought to create an ultra-low risk category in which none of the patients had an abnormal troponin which would not have been possible if we kept the age>65 cut-off. Another important difference is that we redefined metabolic disease in this model as the presence of hypertension and diabetes (excluding hypercholesterolemia from this variable and from analysis). This was done as we included cholesterol-lowering medications as an independent predictor which would be expected to be correlated to hypercholesterolaemia. We did not include vasculopathy in this analysis as age>60 and cholesterol medications were moderately correlated with it. When we ran preliminary analysis

using vasculopathy along the other 22 variables listed above, this variable was not in the derived model. Similarly, when we ran preliminary analysis using vasculopathy along with only either age>60 or cholesterol-lowering drugs and the other 20 variables, vasculopathy was not in the derived model. Lastly, when we ran preliminary analysis without age>60 or cholesterol-lowering drugs along the other 20 variables, the AUC of the retained model was significantly lower. As such, we decided not to include vasculopathy in the abnormal troponin model. We did however include all of the other variables used in the MACE regression analysis including monitored in the ED, final ECG interpretation suggestive of infarction or ischemia not known to be old and QTc>500ms which were variables retained in the MACE LR model. As troponin is mainly used to rule out ischemic cardiac disease, we thought that it was important to include the same predictors with a few changes.

We included other predictors that have been shown to cause troponin elevation without myocardial ischemia such as congestive heart failure, renal failure, pulmonary embolism and atrial fibrillation/flutter. We also included pulmonary system-related variables (shortness of breath accompanying the chest pain episode, abnormal respiratory rate) for the same reasons.

Prior to multivariable regression analysis, the highest Pearson correlation coefficient (0.39) was obtained for age>60 and taking a cholesterol-lowering medication (Appendix 7). Lastly, all tolerance values were ≥ 0.1, variance inflation values were ≤ 10, Eigen values were not close to 0 and their respective condition indices were not elevated (Appendix 8 and 9).

Eleven variables were retained in the derived abnormal troponin model (Table 13). The 3 variables with the highest ORs for an abnormal troponin were congestive heart failure (OR 6.78, 95% CI: 3.13, 14.68), known chronic renal failure (OR 6.47, 95% CI: 2.31, 18.11) and QTc>500ms (OR 5.84, 95% CI: 1.90, 17.99). The variable with the lowest OR for an abnormal troponin was pain radiating to the arm or jaw (OR 1.64, 95% CI: 1.04, 2.58). All retained variables achieved

statistical significance for their association with an abnormal troponin (Table 14). The AUC for this model was 0.89 (95% CI: 0.87, 0.91). Meanwhile, the Hosmer and Lemeshow Goodness-of-Fit-Test was not statistically significant with a Pr > ChiSq = 0.64 and a chi-square of 6.02. A calibration plot for the derived model was built (Figure 4). A ROC curve for the derived abnormal troponin LR model was plotted (Figure 5).

The bootstrapped AUC of the model was 0.89 (95% CI: 0.87, 0.92) (Table 11). The optimism was 0.01 and the optimism-adjusted AUC was 0.88 (95% CI: 0.86, 0.91). Seven out of the eleven variables in the retained model appeared in more than 90% of the bootstraps (Table 15).

4.7 MACHINE LEARNING MODELS

All four ML models had comparable AUCs with CI overlapping those of the corresponding LR models (Table 11). The MACE full ML model using 59 variables had an AUC of 0.92 (95% CI: 0.89, 0.94). Meanwhile the MACE 8-variable ML model using the 8 retained variables with the highest importance had an AUC of 0.90 (95% CI: 0.86, 0.93) (Table 16). The abnormal troponin full ML model achieved an AUC of 0.92 (95% CI: 0.90, 0.93) while the 8-variable ML model using the 8 retained variables had an AUC of 0.90 (95% CI: 0.87, 0.92) (Table 17). ROC curves comparing the full models to the 8-variable models were created (Figure 6 and Figure 7).

4.8 CLINICAL DECISION SCORES

A clinical decision score, named the Preliminary Chest Pain Risk Score (PCPRS), was obtained using the regression coefficients for the predictor variables in the derived MACE LR model (Table 18). In our study, 450 patients (44.4%) would have been considered low risk using this score. None of the patients in this group suffered from a MACE. In the high risk group meanwhile, 47.4% of the 78 patients suffered from a MACE. The clinical decision score was found

to have a sensitivity of 100.00% (95% CI: 94.87%, 100.00%) and a specificity of 47.67% (95% CI: 44.44%, 50.91%) at identifying patients that are medium or high risk of MACE from those that are low risk (Table 19). A high risk score was associated with a 12.17 positive likelihood ratio (95% CI: 8.39, 17.66) of suffering from MACE (Table 20).

A clinical decision score, named the Ultra-Low Risk Troponin Score (ULRTS), was also derived this time using the regression coefficients of the predictor variables in the derived abnormal troponin LR model (Table 21). None of the 104 patients with a score of 0 had an abnormal troponin. The score's sensitivity for identifying ultra-low risk chest pain patients from the other groups was found to be 100.00% (95% CI: 98.38% to 100.00%) and its specificity 14.07% (95% CI: 11.65% to 16.79%) (Table 22).

CHAPTER 5: DISCUSSION

5.1 ENROLMENT

We enrolled 1,014 patients over 43 days or an average of 23.6 patients a day at the two sites. Approximately two thirds of visits to the ED that were labelled as chest pain were included in the study. Most patients were excluded either because they lived outside of the catchment area of our hospital or because they did not have an ECG or troponin done during the visit. We suspect that the patients from outside the Ottawa area had similar past medical history, presented with similar symptoms and suffered from MACE at a similar rate as the patients that we included. In fact, most patients that were excluded because of this resided across a bridge in a different province, in the neighbouring city of Gatineau. As such, it is extremely unlikely for our LR or ML models to have been affected by excluding patients that would have been expected to have similar patient characteristics, presentations and positive outcomes as those in our included study population. Chest pain patients who did not have a troponin or ECG were likely not deemed to be at any risk for ACS by the ED physician who can order these diagnostic tests and as such we are unlikely to have missed any MACE in this patient population.

Although our study period was short, we did record MACE in 70 patients or 6.9% of patients who presented with chest pain. The prevalence of MACE in our chest pain cohort is slightly higher than the 4% acute MI prevalence reported in undifferentiated chest pain patients but we attribute this to reporting a composite outcome which also includes death, urgent revascularization, ventricular arrhythmias and cardiac arrest and also to reporting on MACE not just on index ED visit but up to 6 weeks following the index ED visit. [88]

5.2 LOGISTIC REGRESSION MODELS

The derived MACE LR model is composed of 9 variables, 6 of which have previously been used in the HEART score (smoking history, positive family history of CAD, exertional chest pain, pain radiating to arm or jaw, symptoms relieved by nitroglycerin and an ECG suggestive of ischemia). Two of the three predictors with the greatest weight in our model were interestingly novel variables: monitored in the ED and QTc>500ms. The internally validated model achieved an AUC of 0.89 (95% CI: 0.87. 0.93) while incorporating variables from each of: demographics, initial ED course, past medical history, history of presenting illness, vital signs, and ECG changes. No two groups of variables experienced anything other than low correlation based on the Pearson coefficient (defined as <0.5) and other methods of detecting multicollinearity did not suggest the presence of significant correlation. [104]

With an also excellent AUC of 0.89 (95% CI: 0.87, 0.92), the internally validated abnormal troponin LR model is composed of 11 variables. It incorporated variables from each of the categories of predictors. Interestingly, it also retained the same novel variables from the MACE LR model (abnormal QTc, monitored in the ED and an abnormal systolic blood pressure). Also, tests for multicollinearity did not suggest any significant correlation between any two retained variables.

We do not expect our MACE or abnormal troponin LR models to have been affected by the omission of temperature or oxygen saturation as predictor variables. Temperature has not been reported in literature to be predictive of MACE. An abnormal temperature can be seen with pneumonias, sepsis or myocarditis but the occurrence of these conditions in patients presenting with undifferentiated chest pain is quite low compared with MI. We therefore do not believe that the variable would have been kept in the derived models. Further supporting this is that the ML 8-variable models for MACE and abnormal troponin did not have temperature as a variable with a

high feature of importance. There are several reasons why we think that excluding oxygen saturation from the LR multivariable analysis did not affect the retained models. First, a drop in oxygen saturation is not specific to cardiac ischemia. Second, pulse oximetry which is commonly used to determine oxygen saturation in the ED, is often not accurate as it can be affected by poor perfusion (sepsis, congestive heart failure), anemia and a range of patient factors (dark skin, nail polish). [105] Lastly, although we included a respiratory rate as a potential predictor variable in the derivation of our abnormal troponin model, it was not present in the derived model suggesting that there are more important predictors than respiratory status for an abnormal troponin.

In terms of LR model stability, both the MACE and abnormal troponin models were shown to have a good fit according to Hosmer-Lemeshow goodness of fit test for the data collected. In addition, calibration plots for both models also suggested good fits as the model curves with 95% confidence intervals overlaid the ideal predicted probability to observed outcome curves. The MACE LR model had an EPV of 5.0. The aim of having 10 events for each variable in a LR model has been reconsidered with lower ratios, and as such we did not limit the number of variables in our models to achieve an EPV $\geq$10. [49, 87, 99] A study published in 2006 by Vittinghoff & McCulloch in *The American Journal of Epidemiology*, showed that the maximum type 1 error (rejecting the null hypothesis erroneously) is similar in models with EPVs between 5-9 and models with EPVs between 10-16. [106] The task of removing some predictors to achieve an EPV of 10 or more for the MACE model was also difficult with our current sample size as some predictors for retained variables in the model had similar ORs and we would want to ensure that these ORs do not change significantly in future studies with larger study sizes. Because of the large number of patients with an abnormal troponin in the study (23.4%), the abnormal troponin model had a much higher EPV of 10.3. We do not believe that there was any significant overfitting in the derived models. Additionally, the low optimism variables obtained and the frequent appearance of

retained predictors during internal validation bootstrapping suggests that the models are robust and a good fit.

5.3 MACHINE LEARNING MODELS

The MACE ML models achieved excellent AUCs when using all variables (AUC=0.92, 95% CI: 0.89, 0.94) and when only using 8-variables (AUC=0.90, 95% CI:0.86, 0.93). The AUC obtained by RF methodology to predict MACE is similar to what has been reported in literature. For example, a database study on 1,409 NSTEMI patients published in 2022 by Qin et al., created ML algorithms to predict NSTEMI by using 56 clinical and laboratory features (including contemporary troponin and CK-MB) and reported AUCs of 0.90-0.93 for their RF models. [107] In this same study, a gradient boosted decision tree ML method known as extreme gradient boosting (XGBooth) was shown to develop models with even higher AUCs of 0.91-0.97 using the same patient database. XGBooth works by sequentially creating improved decision trees, fixing errors that the initial decision trees were found to have, until there are no more errors. [108] We would not however have been able to employ this ML method in our study as it requires a large amount of data. As we enroll more patients in our study, we will refine our RF model while seeking to achieve a greater AUC while in tandem exploring the performance of gradient boosted decision trees.

In our 8-variable MACE ML model, three remaining variables were ECG related (ischemia findings). Six of the eight variables with the largest impurity-based importance have been reported in previous CDS. Abnormal systolic blood pressure and an abnormal oxygen saturation meanwhile are variables that have not been previously used in chest pain CDS. An abnormal oxygen saturation may be indicative of a known underlying lung pathology such as COPD or a cardiac-related issue such as heart failure causing pulmonary edema which can be a complication of arrhythmias, valve

disease or large MIs. Aside from ECG related changes, age was the variable with the highest impurity-based importance which is clinically supported by the fact that age is the most important non-modifiable ACS risk factor.

The abnormal troponin ML models also achieved a slightly better AUC when incorporating all variables (AUC=0.92, 95% CI: 0.90, 0.93) than when it only incorporated 8-variables (AUC=0.90, 95% CI: 0.87, 0.92) however the CI overlapped and it is likely that the models have similar performance. The 8-variable model retained variables known to increase the risk of MACE but also congestive heart failure which is associated with an increase in troponin outside of an ACS event due to troponin leak from myocytes instead of cellular death, secondary to the increased intra-cardiac pressures due to fluid overload. [109] The model also included "not taking any medications" as a variable with a high impurity-based feature importance suggesting that people without treatable comorbidities are unlikely to have a troponin elevation. This may be because the incidence of MI is likely lower in what is assumed to be a healthy group of individuals who do not take medications but also because multiple other causes of a troponin elevation such as chronic kidney disease and heart failure are unlikely to be present in patients who do not take any medications. Finally, the 8-variable model also included a final ECG interpreted as normal as a predictor. This can be explained by the fact that patients who do not have signs of ischemia or an abnormal heart rhythm such as atrial fibrillation/flutter leading to hypoperfusion of the cardiac myocytes are unlikely to have troponin elevations in the blood stream. Similarly, patients with a normal ECG likely do not have an electrolyte disturbance such as hyperkalemia, which is often precipitated by renal failure, a well-documented cause of increased troponin concentration. [110, 111]

5.4 COMPARISON OF LR AND ML MODELS

To our knowledge, our study is the first to compare LR with ML in the diagnosis of MACE in patients presenting with atraumatic chest pain without the use of troponin. The different statistical techniques yielded excellent models with similar AUCs. The models outperform or match previously derived ACS scores that are commonly used in the ED such as TIMI (c=0.65), Grace (c=0.83) and HEART Score (c=0.90). [112]

Although the ML model replaced missing continuous variables (missing vital signs) by the mode while the LR model assumed that the missing variables were likely normal, we do not believe that this affected the integrity of the LR model as the median, mode and mean of all recorded vital signs would have been categorized as normal based on our cut-offs (Appendix 10). We do however expect to have lost some power by categorizing continuous variables. This was done to satisfy the ease-of-use criterion when developing a CDS.

The ML technique developed a MACE model that retained not only different variables but also fewer variables while achieving greater AUCs compared with the respective LR models however as confidence intervals overlapped this difference is not statistically significant. As only the final interpretation of the ECG was used in the LR model, we reran the analysis with specific new changes on ECG (new ST changes, new t-wave inversions, new bundle branch blocks and new pathological q waves) as used with the ML model. None of the specific ECG changes were retained in the final MACE LR model and consequently the AUC of the LR model did not change. Similarly, we reran the abnormal troponin LR model with specific new ECG changes and the derived model did not incorporate specific new ECG changes retaining only the final ECG impression. We chose not to include the new ischemic changes on the second ECG done in the ED variable as we wanted to derive MACE and abnormal troponin CDS that only relied on data from the first ECG as this allows physicians to determine patient disposition earlier during the visit. We did rerun the multivariable analysis with this variable alongside the other 14 variables and although

this new variable was present in the derived model alongside the 9 variables that were present in the original derived MACE LR model, the AUC did not improve (AUC=0.89) and the CI slightly widened (95% CI: 0.86, 0.93).

5.5 PRELIMINARY CHEST PAIN RISK SCORE

The PCPRS is a prognostic CDS which includes well documented CAD risk factors (smoking and positive family history of CAD) as predictors of MACE in chest pain patients. The main advantage of the PCPRS is that unlike the other scores, it does not require any laboratory testing such as a troponin allowing for the earlier risk stratification of chest pain patients. Interestingly, it also incorporates variables that have not previously been used in chest pain CDS.

A prolonged QTc in the absence of a coronary blockage has commonly been know to predispose patients to arrhythmias, such as torsades de pointes which can lead to ventricular fibrillation and ultimately death, by allowing for early depolarization of the myocardium to occur during the repolarization phase. [113, 114] In our model, this variable had the highest OR for MACE and was retained in 95.6% of bootstraps during internal validation. We do not believe that this is due solely to including arrhythmias in our composite outcome as we only recorded arrhythmias that were due to an ischemic event. Instead, patients with prolonged QTc can have conduction abnormalities due to prior cardiac arrests, electrolyte abnormalities or take medications that can prolong the QTc. As such, an abnormal QTc may have served as a surrogate for serious conditions or diseases that was not captured by our list of variables but that increase the odds of MACE. A prolonged QTc as a predictor of MACE, is supported by a recent prospective study which enrolled patients with NSTEMIs and reported that a prolonged QTc was not only predictive of 30-day MACE but also outperformed the TIMI score in this regard and was corelated to peak troponin elevation during an MI. [115]

Monitored in the ED is also a novel variable that has not been quoted in literature as an independent risk factor for MACE. We assume that the decision of placing a patient on a monitor by either the nurse or physician indicates that the patient has a combination of a worrisome past medical history, history, vital signs and physical exam that warrants the patient to be more closely monitored while awaiting results of diagnostic tests. The high odds ratio with this variable is reminiscent of other validated clinical decision rules such as the Canadian Syncope Risk Score and the Wells Score which rely heavily on clinical gestalt. [96, 116]

The HEART and ADAPT scores do not use any vital signs as predictors of MACE. The PCPRS however uses an abnormal systolic blood pressure. An abnormal systolic blood pressure in the ED could be a marker of poorly treated hypertension, a well documented risk factor for MACE. It could also be indicative of ACS in the acute setting as studies have shown that in the absence of known hypertension, 31.7% of patients admitted for ACS had a systolic blood pressure greater than 160. [117] This may be due to the sympathomimetic compensatory response through which the body tries to overcome an obstructed coronary artery by releasing catecholamines causing an increase in the pressure of the blood proximal to the obstructed vessel. A low blood pressure meanwhile may be indicative of cardiac pump failure secondary to a massive MI or to an arrhythmia.

Other components of the PCPRS have been well documented to increase the risk of MACE. Smoking has been shown in prior studies to increase the risk of MI by a larger amount than other modifiable risk factors including diabetes, hypertension, and obesity. [118] Meanwhile, a family history of CAD has been shown in other studies to not only significantly increase the odds of an MI but also to synergistically interact with other risk factors such as hypertension and hypercholesterolemia to further increase the odds of MI. [119] Our score is also one of the first chest pain scores to include and score specific historical components, well-described in medical literature to increase the likelihood of an MI, such as exertional chest pain and pain radiating to

the arm or jaw. [120] Although the HEART score does classify history as non-specific, moderately suspicious or highly suspicious, it does not score individual historical elements. For this reason, inter-rater variability for the score may be lower than what we would expect with the PCPRS. Our score also includes an ECG suggestive of ischemia with an appropriately elevated OR for a MACE. Unlike the HEART Score which would classify a patient with isolated ischemia on their ECG, the PCPRS classifies the same patient as moderate risk which is more appropriate.

When determining the cut-off score for low risk patients in the PCPRS, it was decided that scores of 0-2 would be included as none of the patients with these scores suffered from a MACE. We considered including patients with a score of 3 in the low risk category as only 7 patients out of 178 with this score had a MACE increasing the low risk category MACE estimated risk to 1.10%. We decided against it however as patients with isolated exertional chest pain or an ECG suggestive of ischemia would have been categorized as low risk. A lower cut-off increased our sensitivity to 100.00% (95% CI: 94.87%, 100.00%) but decreased our specificity to 47.67% (95% CI: 44.44% to 50.91%). In most CDS developed for the ED, an increased sensitivity is desirable over a higher specificity or accuracy as the ED physician's main goal is to rule out disease. Despite this, the sensitivity and specificity of the PCPRS in identifying low risk patients is comparable to the 95.9% (95% CI: 93.3%-97.5%) sensitivity and 44.6% (95% CI: 38.8%-50.5%) specificity of the HEART score reported in a recent meta-analysis but has the added benefit of not requiring a troponin to be drawn prior to calculating a score. [121] Lastly, the PCPRS categorizes 44.4% of undifferentiated chest pain patients as low risk whereas the HEART score is reported in the literature to categorize a lower percentage of chest pain patients as low risk (<35.0%). [53, 122]

Once externally validated, ED physicians would be able to use the PCPRS to risk-stratify atraumatic chest pain patients. A low risk score would support the decision of the ED physician to safely clear the patient from an ACS diagnosis. Meanwhile, a medium risk score in a patient with

a normal troponin (not having an active MI) and without dynamic ECG changes, would require risk stratification within 48 hours either by directly consulting the cardiology service or by ensuring that the patient has a stress test or angiography. Lastly, a high score would require a mandatory cardiology consultation for admission and in-patient risk stratification.

5.6 ULTRA-LOW RISK TROPONIN SCORE

Our study is also the first to present a diagnostic CDS to predict which patients will have an abnormal troponin before it is even drawn which we expect once validated, to have the potential to decrease the proportion of ED patients with chest pain that require bloodwork. The ULRTS contains many of the same predictors that the PCPRS included such as monitored in the ED, exertional chest pain, pain radiating to the arm or jaw, final ECG impression suggestive of ischemia or infarction not known to be old and a QTc>500ms. As these predictors have been shown in our study to be associated with MACE, it is not surprising to also have them as predictors of an abnormal troponin which in some cases is suggestive of an acute MI. Other predictors used in the ULRTS have been shown to increase the troponin concentration in patients that were not suffering from an acute MI such as congestive heart failure (due to troponin leak from cardiac myocytes), chronic renal failure (due to decrease clearance of troponin), male sex (due to a larger number of myocytes) and advanced age (multifactorial, likely secondary to comorbidities). [123-125]

Applying the ULRTS to our study population, 104 patients or 10.8% of patients who had a troponin drawn, could have been cleared from an ACS standpoint without having to draw up bloodwork. Of these 104 patients, none had a MACE during the study period. Median troponin turnaround time can range from 57 to 74 minutes from the time the blood is collected to the time the test has resulted [126]. Reducing the need for a troponin to be drawn would reduce length of stay by at least one hour for about one tenth of patients, who would be considered as ultra-low risk

and would not require a troponin draw to rule out ACS. The one-hour savings per ultra-low risk patient is a conservative estimate however as patients are seldom discharged immediately after a test is available due to constraints in human resources.

We envision the ULRTS score, one externally validated, to allow physicians to forego troponin testing in ultra-low risk patients. A patient with a score greater than 0 will still require troponin testing to be cleared from an ACS diagnosis.

5.7 ADVANTAGES OF PCPRS AND ULRTS OVER ML ALGORITHM

An advantage of the PCPRS and ULRTS scores is that they can easily be used by physicians without the need for any computing hardware or software. They can also easily be shared across geographical boundaries and are intuitive with clear explanations of the proportional weighing of each variable resulting in much less steep learning curves than the algorithms built by ML which have been described by some as mysterious "black boxes". Unlike the ML algorithms, the PCPRS and ULRTS scores were derived using variables from most categories of predictors akin to what physicians typically do when estimating the risk of a certain disease or abnormal test in a patient. This makes the scores much more intuitive and logical to use. In our small sample size, the ML algorithms may be prone to overfitting but it is hoped that by expanding the study sample size and consequently the number of outcomes, this will no longer be considered to be an issue.

As EMR design improves and either allows for the direct integration of ML algorithms within a patient's chart or the seamless extraction of data from a patient's chart into a software containing ML algorithms that can automatically calculate risks of various diseases, it is expected that ML algorithms will have an edge over clinical decision scores requiring provider input and calculation. It is envisioned that in the future, physicians will be able to use automatically

generated risk scores in their discussions with patients as part of the shared-decision making process. Also, physicians working at a computer station may be prompted by alerts displaying the instantaneously-calculated risk score of life-threatening diseases as additional information is typed into a patient's chart. This alert would encourage the physician to consider additional investigations, consultations or follow-up for their patient. It is also expected that in the future the input of information into EMRs and consequently the ML algorithms which will provide risk scores will be simplified by emerging technologies such as natural language processing (NLP), which can automatically recognize spoken words, wearables which can provide constant monitoring of vital signs and improved image-recognition software that can recognize abnormal breathing patterns, movements and behaviours associated with certain diseases.

5.8 STRENGTHS

Our study retrospectively enrolled over 1,000 patients at two sites and collected data from multiple categories (demographic, initial ED course, past medical history, medications, history of presenting illness, vital signs and ECG interpretation) known to increase the risk of ACS. It analyzed the historical component of patient charts by dichotomizing clearly defined characteristics of chest pain that can either increase or decrease the likelihood of ACS based on previously published data. Also, all troponin bloodwork was done using the same high-sensitivity assay and we recorded all troponin results before a disposition decision was made by the ED physician ensuring that we captured an abnormal troponin value if it occurred. Data was missing for few vital sign variables and we did not rely on multiple imputation. We assured systematic follow-up via our institution's EMR which covers the two largest hospitals in the city of Ottawa and limited the possibility of lost to follow-up by only enrolling patients that are from catchment

area of The Ottawa Hospital. After deriving the LR and ML models we successfully internally validated their performance using bootstrapping.

The PCPRS that we derived contains variables found in the HEART score (history, ECG, risk factors) but more clearly describes and scores historical component variables associated with MACE. The score also uses novel variables (abnormal QTc and monitored in the ED) which are clinically plausible to be associated with MACE. Most importantly, the PCPRS is the first undifferentiated chest pain CDS that can achieve an excellent AUC of 0.89 without the use of troponin.

An additional strength is that the LR and ML models were built in isolation by different researchers with access to the same data who were blinded until the very end to the performance of the other model that was being compared.

5.9 LIMITATIONS

Our study is not devoid of limitations. It is retrospective and only enrolled patients over a couple of months at two urban academic hospitals that are part of the same institution. We assumed that if an element in the past medical history, medication or history of the presenting illness was not listed in the physician's note, it was likely not present in the patient. We however have no way of truly knowing if the question was indeed asked by the physician and if the patient truly did not have the medical condition/take the medication/have the symptom characteristic. We did partially remedy this situation by also reviewing consultant or admission notes from the index ED visit. These notes tend to be more complete and, in many cases, confirmed the absence of certain medical conditions, medications or symptom characteristics.

Although we collected data on medications as possible surrogates for disease, we refrained from making specific inferences about disease prevalence in the study population based on medications choosing instead to include the specific medications rather than the diseases that they are designed to treat in the MACE LR model. For the abnormal troponin LR model, we chose to include the use of cholesterol-lowering medications rather than hypercholesterolemia as statins are known to cause rhabdomyolysis of skeletal muscle, elevate troponin levels after moderate exercise but other studies have shown that they lower the concentration of troponin. [127, 128] As they have an unclear role in affecting troponin levels, we thought that it would be more useful to include the medication rather than the disease itself in the model. We therefore expect that there is a negligible risk of misclassification with the LR models. This however comes at the cost of underestimating the prevalence of certain diseases in the population if physicians omitted to document thorough past medical histories.

Furthermore, ECGs were interpreted by a single physician researcher. We also chose to transform continuous variables into categorical variables for the LR models to make the PCPRS and ULTRS more user-friendly. This however did come at the cost of reducing statistical power and could have also masked non-linear relationships between the predictor variable and the outcome. [129] Interestingly, despite this, the ML algorithms which kept continuous variables in their original format, were not found to outperform the LR models. Moreover, we did not assess inter-observer reliability for the data that was collected although we did perform quality checks on randomly selected charts throughout the data collection stage. In addition, data abstractors who collected information on predictors were not blinded to the outcomes however were encouraged to only record outcomes after all predictors had been collected.

Also, as most MACE were reported on the index ED visit and only 8.6% of MACE occurred within 6 weeks of the visit, it is expected that our score will perform particularly well at

determining which patients will have a MACE on index visit rather than which will have one during short-term follow-up although more studies are needed to confirm this. Moreover, follow-up of cases was only done using the local EMR and as such there is a possibility that some outcomes could have been missed if a patient presented to another hospital or died without being indicated in the medical records. We did try to limit lost to follow-up cases by excluding patients that did not reside in the Ottawa area.

Finally, although we included over 1,000 patients, studies developing ML algorithms are typically trained on larger populations and it would be expected that their performance would improve further with a larger data set.

CHAPTER 6: CONCLUSION & FUTURE DIRECTIONS

When comparing LR with ML derived models to predict MACE in undifferentiated chest patient patients, both techniques yielded similar results. LR and ML models were also found to have a similar performance in predicting which undifferentiated chest pain patients are likely to have an abnormal troponin during their ED visit. The novel PCPRS was found to perform at least as well as the HEART score with the added benefit of not having to rely on a troponin value for risk calculation which is a novelty amongst previously published undifferentiated chest pain CDS. The PCPRS also incorporates new predictor variables (abnormal QTc, monitored in the ED, systolic blood pressure <90 or >160mmHg) which have not been previously used in other chest pain or ACS CDS. The ULRTS meanwhile is the first CDS to predict which patients are likely to have an abnormal troponin result allowing ultra-low risk patients with chest pain to be cleared from an ACS standpoint without drawing bloodwork. Both derived models performed well during internal validation by bootstrapping.

In future studies, we will first seek to externally validate the LR and ML models and scores presented in this manuscript by prospectively recruiting a larger cohort of chest pain patients in a multisite study. Once validated, we aim to implement the CDS at both academic and community hospitals outside of the Ottawa area. In the implementation study, we plan on having the scores integrated directly into local EMRs to automatically calculate risk for the clinician assisting them in faster and safer care for undifferentiated chest pain patients. Finally, we are interested at evaluating the performance of ML when using unstructured data by applying NLP to histories of presenting complaint followed my ML techniques to develop predictive algorithms using raw data from the patient's chart rather than categorical data extracted by researchers.

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TABLES & FIGURES

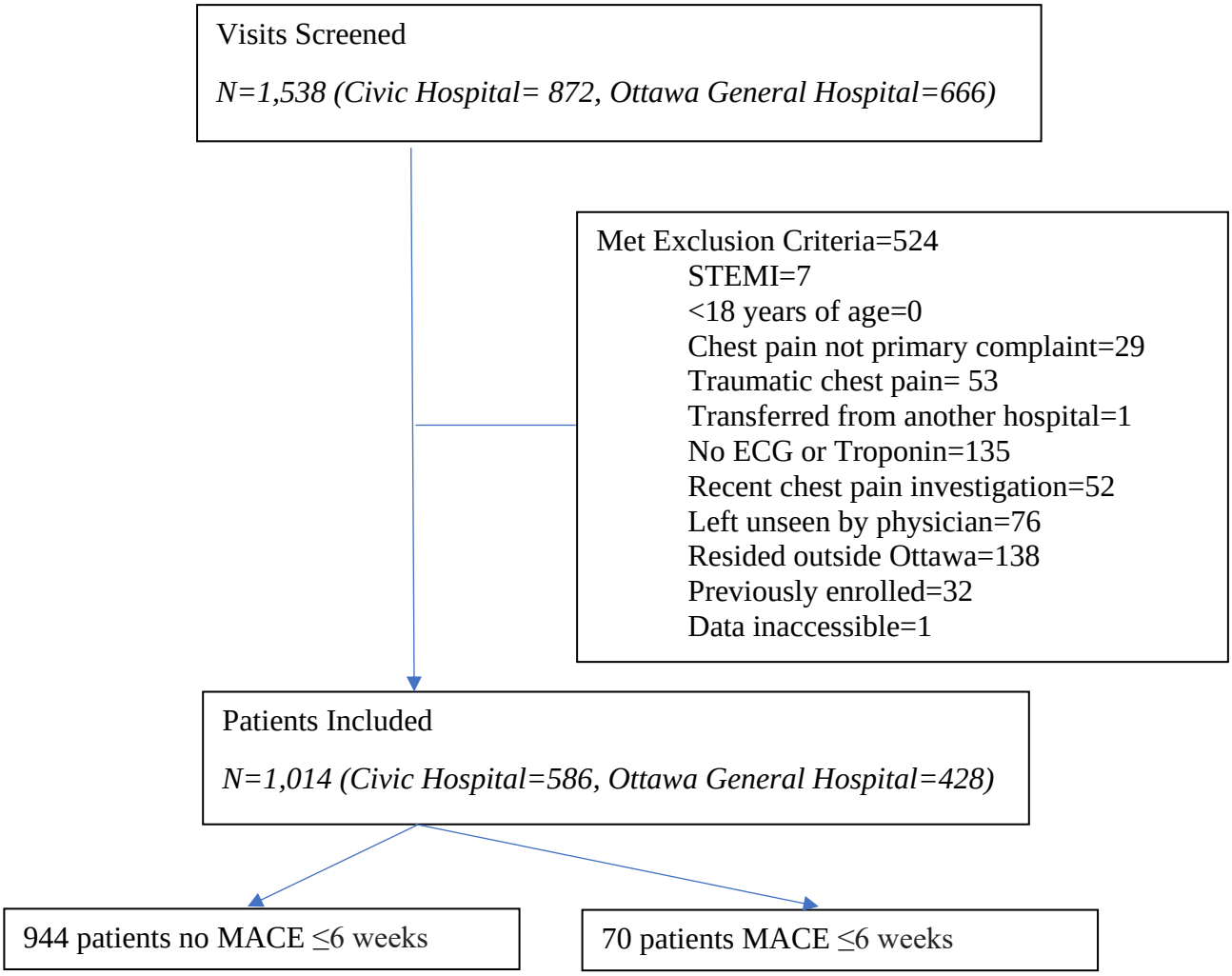


Figure 1. Study flow chart.
MACE: Major adverse cardiac events

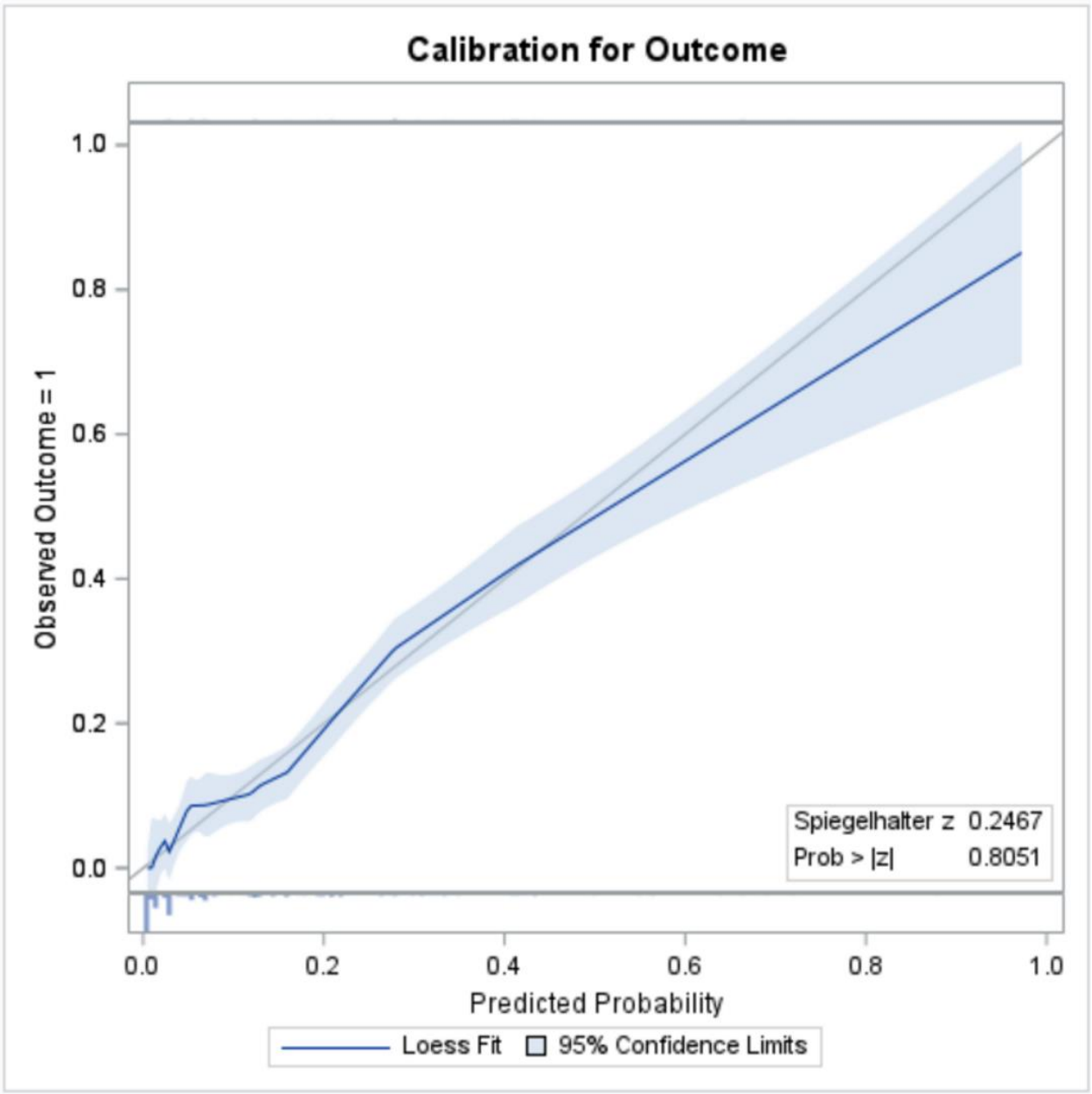


Figure 2. Calibration plot for the derived major adverse cardiac events logistic regression model. Smoothing parameter = 0.3 was chosen in lieu of automatic smoothing.

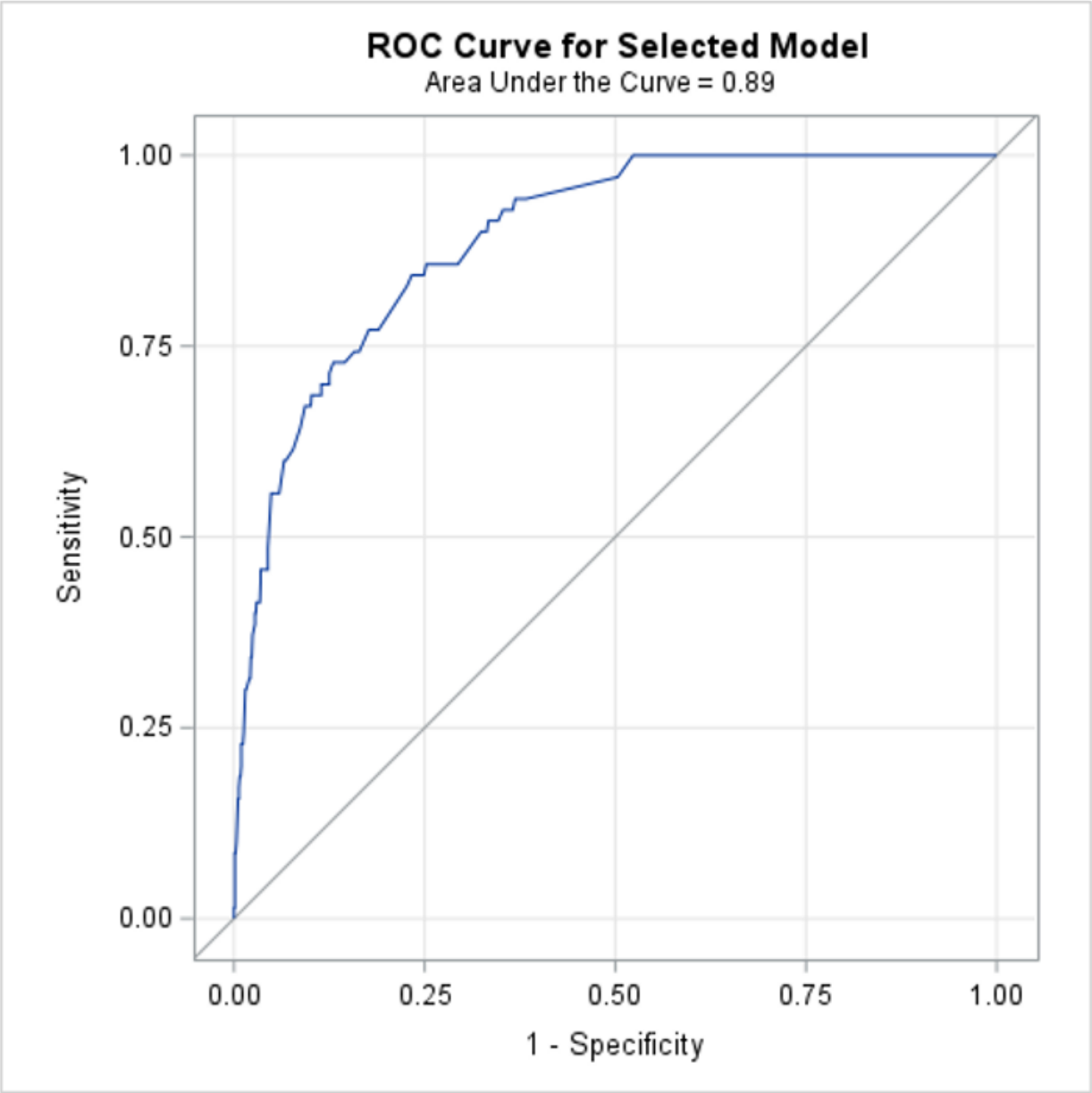


Figure 3. Receiver-operator characteristic curve for the derived major adverse cardiac events logistic regression model.

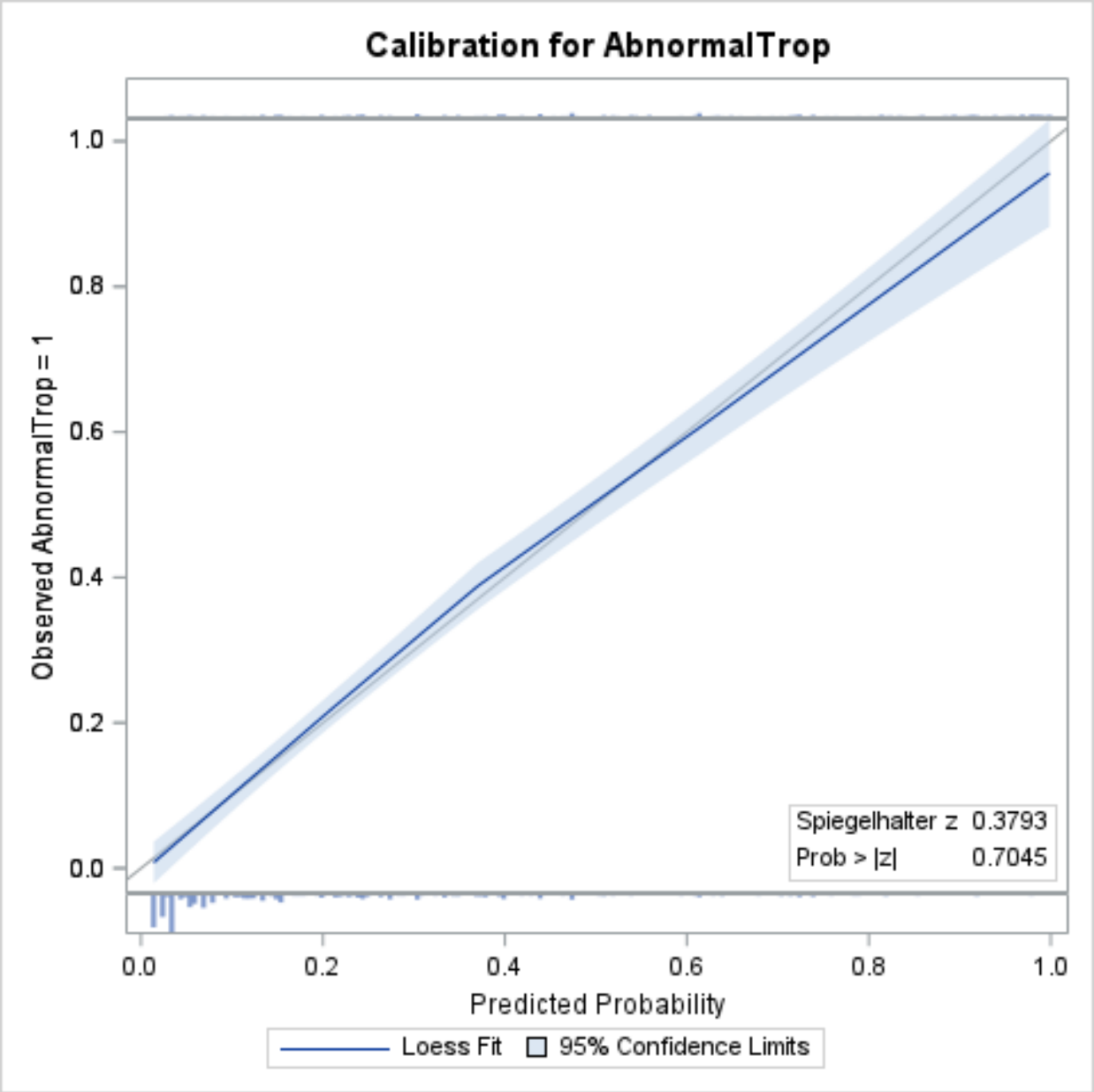


Figure 4. Calibration plot for the derived abnormal troponin logistic regression model.

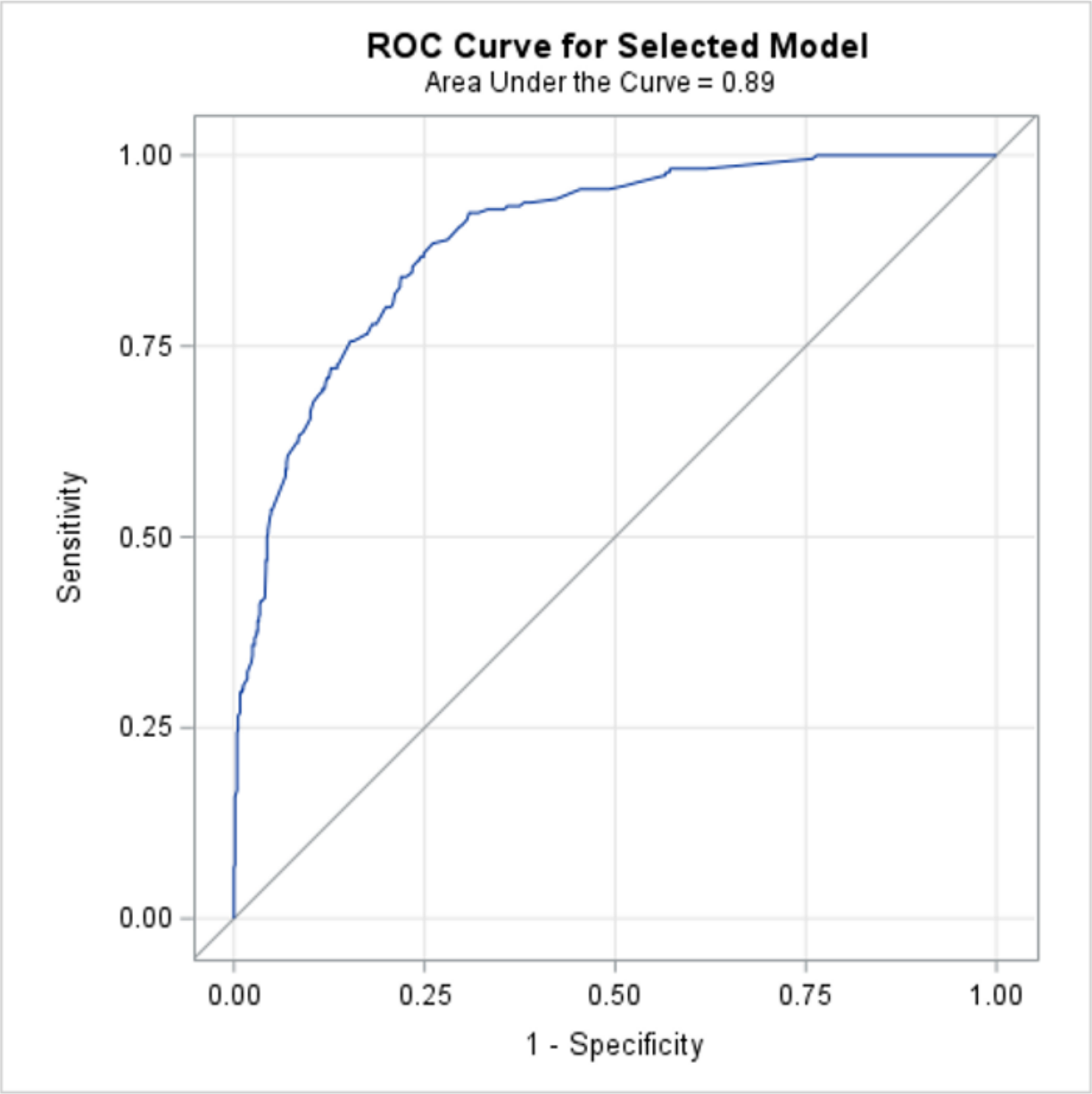


Figure 5. Receiver-operator characteristic curve for the derived abnormal troponin logistic regression model.

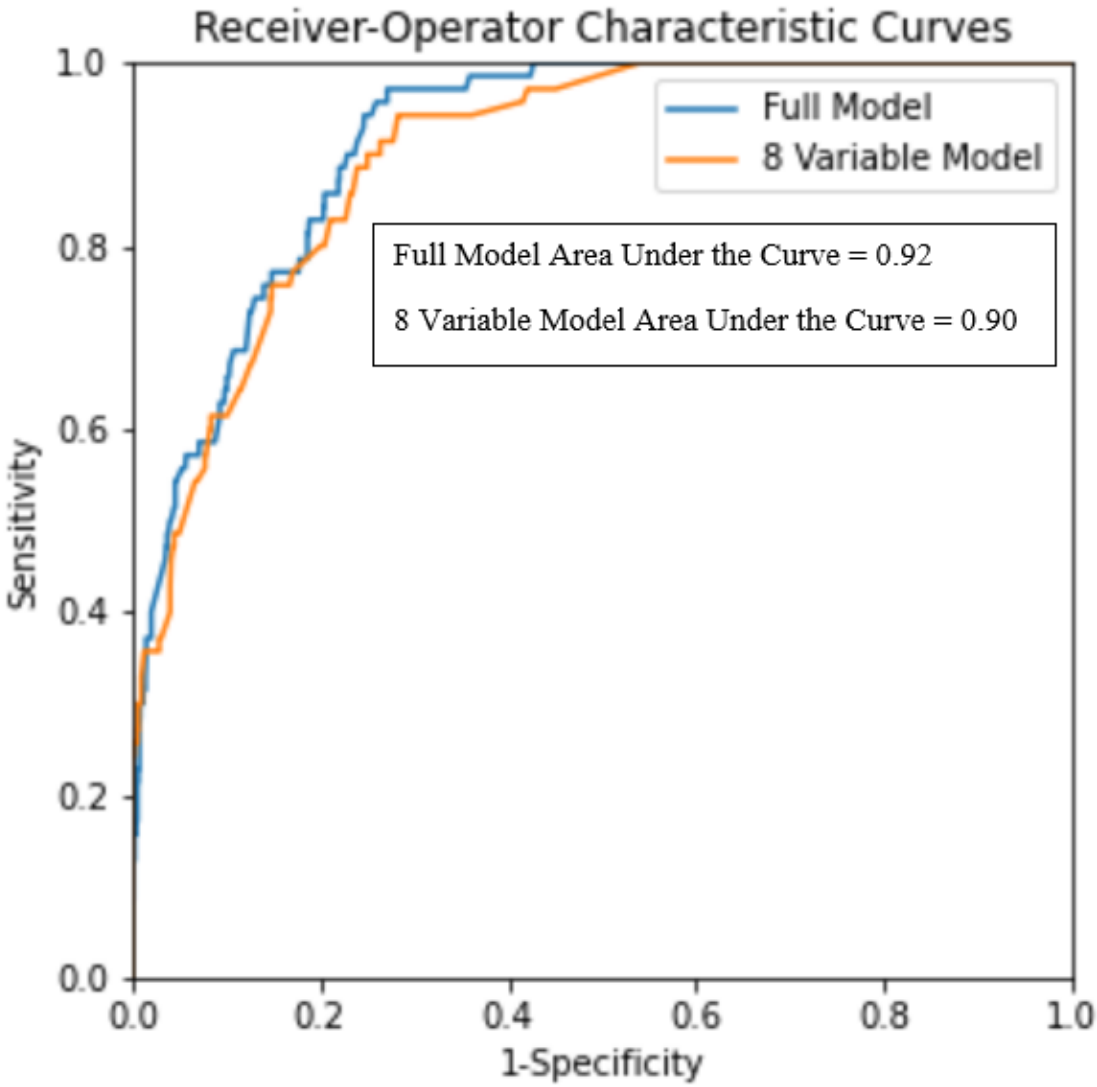


Figure 6. Receiver-operator characteristic curves for the major adverse cardiac events machine learning full and 8-variable models.

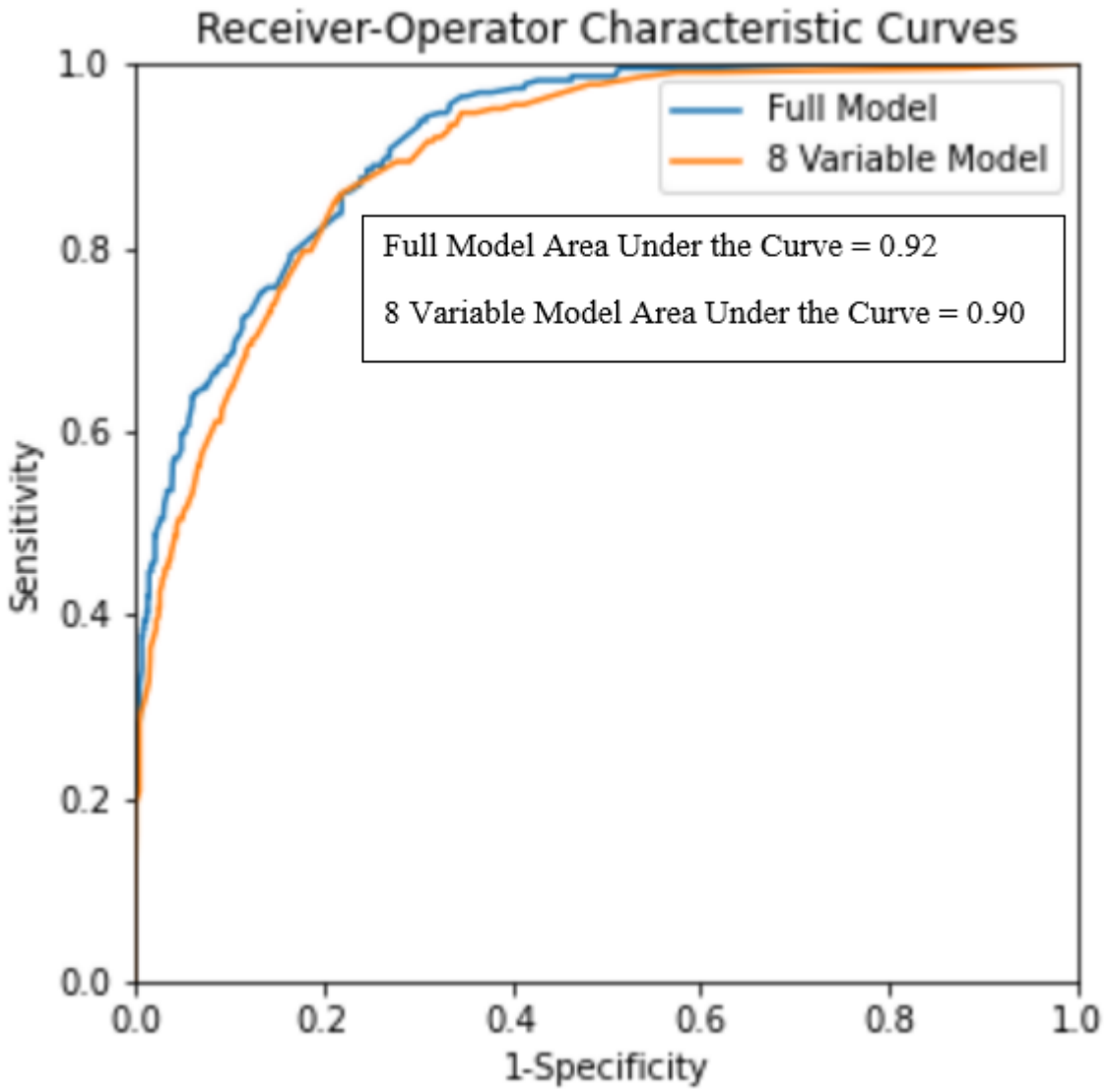


Figure 7. Receiver-operator characteristic curves for the abnormal troponin machine learning full and 8-variable models.

Table 1. Demographic, initial emergency department course and medical history of patients included in the study.

Patient Characteristics	***N*=1014**
Demographics	
Age (years)	
Mean (±SD)	55.7 (±18.2)
Range	18-99
Median (Q1, Q3)	56 (42, 69)
Males	491 (48.2)
Initial Emergency Department Course	
Arrival by ambulance	243 (24.0)
Monitored in the emergency department	450 (44.4)
Past Medical History	
Smoking status	
Never smoked or information not available	669 (66.0)
Previous smokers	139 (13.9)
Active smokers	194 (19.1)
Coronary artery disease	243 (24.0)
Angina	45 (4.4)
Family history of coronary artery disease	88 (8.7)
Prior smoker	139 (13.7)
Chronic obstructive pulmonary disease	54 (5.3)
Hypertension	400 (39.5)
Diabetes	168 (16.6)
Hypercholesterolemia	303 (29.9)
Transient ischemic attack	33 (3.25)
Cerebrovascular accident	44 (4.3)
Obesity	177 (17.5)
Peripheral vascular disease	26 (2.6)
Congestive heart failure	64 (6.3)
Implantable cardioverter-defibrillator /Pacemaker	28 (2.8)
Renal failure	46 (4.5)
Ventricular arrhythmia	27 (2.7)
Atrial fibrillation/flutter	84 (8.3)
Cardiac arrest	12 (1.2)
Pulmonary embolism	21 (2.1)
None of the above	289 (28.5)
Medications	
Aspirin	226 (22.3)
Clopidogrel or ticagrelor	64 (6.3)
Other anticoagulants	102 (10.0)
Beta blockers	208 (20.5)
Calcium channel blockers	139 (13.7)
Nitroglycerin or other nitrates	102 (10.1)
ACE inhibitors/Angiotensin receptor blockers	225 (22.2)
Cholesterol-lowering medications	306 (30.2)
None of the above	540 (53.3)

Table 2. Chest pain characteristics and associated symptoms as noted in the history of presenting illness section of the physician note.

Chest Pain Characteristic	
Crushing/Pressure	230 (22.7)
Exertional or relieved by rest	130 (12.8)
Radiates to jaw or arm	243 (24.0)
Single episode	137 (13.5)
Ongoing symptoms	302 (29.8)
Relieved by nitroglycerin	63 (2.6)
Middle or left sided	599 (59.1)
Pleuritic	169 (16.7)
Positional	129 (12.7)
Tearing	5 (0.5)
Associated Symptoms	
Shortness of breath	306 (30.2)
Diaphoresis	91 (9.0)
Gastrointestinal symptoms (nausea or vomiting)	145 (14.3)
Cough	129 (12.7)
Fever	27 (2.7)

Table 3. Vital signs.

	n, (%)	**Missing Data (%)**
Heart rate <60 or >100 beats per minute	186 (18.3)	9 (0.9)
Respiratory rate <12 or >20 breaths per minute	21 (2.1)	18 (1.8)
Systolic blood pressure <90 or >160mmHg	189 (18.6)	13 (1.3)
Diastolic blood pressure <60 or >100mmHg	108 (10.7)	13 (1.3)
Temperature <35°C or >38°C	121 (11.9)	107 (10.6)
Oxygen saturation <95%	81 (8.0)	23 (2.3)
Presence of supplemental oxygen	11 (1.1)	139 (13.7)

Table 4. Electrocardiogram characteristics and measurements.

Electrocardiogram characteristics			**n=1004**
Rhythm			
Sinus			948 (94.4)
Supra-ventricular tachycardia			1 (0.1)
Atrial fibrillation			37 (3.7)
Atrial flutter			6 (0.6)
Junctional			1 (0.1)
Paced			9 (0.9)
Other			2 (0)
Ventricular tachycardia/fibrillation			0 (0)
Multifocal atrial tachycardia or idioventricular			0 (0)
Non-sinus rhythm not known to be old			22 (2.2)
Morphologies			
ST-segment depression			35 (3.5)
Less than ½ mm in at least 2 contiguous leads			3 (0.3)
½ to 1 mm in at least 2 contiguous leads			9 (0.9)
Greater than 1mm in at least 2 contiguous leads			23 (2.3)
T-wave inversion			68 (6.8)
>0.2 mm in 2/more contiguous leads with dominant R waves			42 (72.4)
<0.2 mm in 2/more contiguous leads with dominant R waves			16 (27.6)
Left bundle branch block			23 (2.3)
Right bundle branch block			29 (2.9)
Pathological Q waves			40 (4.0)
Not know to be old morphologies			
ST segment depressions			17 (1.7)
T wave changes			20 (2.0)
Pathological q wave			8 (0.8)
Complete left bundle branch block			1 (0.1)
Complete right bundle branch block			12 (1.2)
Final interpretations			
Normal			667 (65.8)
Nonspecific ST-T wave changes			123 (12.1)
Abnormal but not diagnostic of ischemia			143 (14.1)
Infarction or ischemia known to be old			26 (2.6)
Infarction or ischemia not known to be old			45 (4.4)
Uninterpretable			0 (0.0)
New ischemic changes on second electrocardiogram done in the emergency department			10 (1.0)
Electrocardiogram measurements			
Variable	**Median (Q1, Q3)**	**Mean (±SD)**	**Range**
Heart rate (bpm)	73 (53, 93)	75.5 (±17.0)	38-199
PR interval (ms)	156 (123, 189)	160.4 (±28.6)	72-456
QRS axis (°)	33 (-28, 94)	29.6 (±44.4)	-131-264
QRS interval (ms)	90 (74, 106)	95.6 (±20.0)	58-214
QTc interval (ms)	428 (389, 467)	431.1 (32.8)	319-625

Table 5. Troponin results.

Troponin result	**n=965**
Initial high sensitivity troponin ≤14ng/L	745 (77.2)
Initial high sensitivity troponin >14ng/L	220 (22.8)
Any high sensitivity troponin >14ng/L	226 (23.4)

Table 6. Summary of primary outcomes.

Timing of outcome	**n=70**
Index emergency department visit	59 (84.3)
After index emergency department visit but before end of 6 weeks	6 (8.6)
Both on index and after the emergency department visit	5 (7.1)
Type of primary outcomes irrespective of timing	
Stent revascularization procedure	41 (58.6)
Coronary artery bypass grafting revascularization procedure	14 (21.4)
Non-ST elevation myocardial infarction	5 (7.1)
Death due to cardiac or unknown cause	4 (5.7)
Unstable angina	4 (5.7)
Cardiac arrest	2 (2.9)

Table 7. Detailed major adverse cardiac events in the study population.

Patient #	Index ED Visit				6 Week Follow-Up	
	Primary MACE	Additional MACE (#1)	Additional MACE (#2)	Additional MACE (#2)	Primary MACE	Additional MACE (#1)
1	PCI	NSTEMI				
2	PCI	NSTEMI				
3	PCI	NSTEMI				
4	CABG	NSTEMI				
5	PCI	NSTEMI				
6	NSTEMI				Death (unknown cause)	
7	NSTEMI				PCI	
8	PCI	NSTEMI				
9	PCI	NSTEMI	Ventricular arrhythmia			
10	PCI	UA				
11	CABG	NSTEMI				
12	PCI	UA				
13	PCI	NSTEMI				
14	UA				UA	
15					PCI	STEMI
16	PCI	NSTEMI				
17	CABG	NSTEMI				
18	PCI	NSTEMI			PCI	
19	PCI	UA				
20	CABG	UA				
21	PCI	NSTEMI				
22	CABG	NSTEMI				
23	CABG	UA				
24	UA					
25	NSTEMI					
26	UA					
27	PCI	NSTEMI				
28	NSTEMI				PCI	
29	PCI	STEMI				
30	PCI	NSTEMI				
31	PCI	NSTEMI				
32	NSTEMI					
33	PCI	UA				
34	PCI	Cardiac Arrest	Ventricular Arrhythmia			
35	CABG	NSTEMI				

36					PCI	
37	PCI	UA				
38	CABG	NSTEMI				
39	PCI	UA				
40	PCI					
41	PCI	NSTEMI				
42	PCI	UA				
43	CABG	NSTEMI				
44					Death (unknown cause)	
45	Death (cardiac cause)	Cardiac Arrest	Ventricular arrhythmia			
46	PCI	NSTEMI				
47					NSTEMI	
48					PCI	UA
49	PCI	NSTEMI				
50	PCI	UA				
51	CABG	NSTEMI				
52	PCI	NSTEMI				
53	PCI	UA				
54	PCI	UA				
55	CABG	NSTEMI				
56	PCI	NSTEMI				
57	CABG	Cardiac Arrest	Ventricular arrhythmia	STEMI		
58	PCI	NSTEMI				
59	CABG	UA				
60	NSTEMI					
61	PCI	NSTEMI				
62	PCI	UA				
63	NSTEMI					
64					Death (unknown cause)	
65	PCI	NSTEMI				
66	PCI	NSTEMI				
67	UA					
68	PCI	STEMI				
69	CABG	NSTEMI				
70	CABG	NSTEMI				

PCI=percutaneous coronary intervention, CABG=coronary artery bypass grafting, NSTEMI=non-ST elevation myocardial infarction, UA=unstable angina

Table 8. Patients with non-acute coronary syndrome life-threatening diagnoses on index ED visit.

System	Diagnosis	Prevalence (% total study population)
Cardiac	Third-degree heart block	1 (0.1)
	Ventricular fibrillation not due to coronary stenosis	1 (0.1)
Pulmonary	Pulmonary embolism	6 (0.6)
	Pneumothorax	1 (0.1)
	Lung mass	1 (0.1)
Gastro-intestinal	Cholecystitis	1 (0.1)
	Appendicitis	1 (0.1)
Neurological	Transient ischemic attack	3 (0.3)
Other	Sepsis	1 (0.1)
	Diabetic ketoacidosis	1 (0.1)

Table 9. Variables and their respective odds ratio in the derived major adverse cardiac events logistic regression model.

Variable	**OR (95% Wald Confidence Limits)**
Monitored in the emergency department	5.55 (2.53, 12.16)
Active smoker	1.97 (1.08, 3.58)
Family history of coronary artery disease	3.14 (1.42, 6.96)
Exertional or relieved by rest	5.40 (2.91, 10.01)
Radiates to jaw or arm	2.93 (1.61, 5.31)
Relieved by nitroglycerin	2.70 (1.25, 5.84)
Systolic blood pressure <90 or >160mmHg	2.41 (1.31, 4.44)
Final electrocardiogram interpretation suggestive of infarction or ischemia not known to be old	8.73 (3.94, 19.33)
QTc>500ms	10.07 (3.38, 30.06)

Table 10. Analysis of maximum likelihood estimates in the major adverse cardiac events logistic regression model.

Parameter	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept	-5.6082	0.4597	148.814	<.0001
Monitored in the emergency department	1.713	0.4008	18.267	<.0001
Active smoker	0.6796	0.3041	4.9935	0.0254
Family history of coronary artery disease	1.1453	0.4053	7.9866	0.0047
Exertional or relieved by rest	1.6858	0.315	28.6415	<.0001
Radiates to jaw or arm	1.0734	0.3046	12.4199	0.0004
Relieved by nitroglycerin	0.9943	0.3935	6.3849	0.0115
Systolic blood pressure <90 or >160mmHg	0.8785	0.3125	7.9012	0.0049
Final electrocardiogram interpretation suggestive of infarction or ischemia not known to be old	2.1665	0.4058	28.5052	<.0001
QTc>500ms	2.3097	0.5579	17.1425	<.0001

Table 11. Performance of logistic regression and machine learning models for major adverse cardiac events and abnormal troponin after bootstrapping the original dataset.

Outcome of Interest	Model	AUC (95% CI)
Major adverse cardiac events	Logistic regression	0.89 (0.87, 0.93)
	Machine learning full	0.92 (0.89, 0.94)
	Machine learning 8-variable	0.90 (0.86, 0.93)
Abnormal troponin	Logistic regression	0.89 (0.87, 0.92)
	Machine learning full	0.92 (0.90, 0.93)
	Machine learning 8-variable	0.90 (0.87, 0.92)

Table 12. Frequency of variable selection during the 500 sample bootstrapping internal validation procedure of the major adverse cardiac events logistic regression model.

Variable	**Frequency**	**% of bootstraps**	**OR in Derived Model**
Exertional pain or relieved by rest	498	99.6	5.40
Final electrocardiogram interpretation suggestive of infarction or ischemia not known to be old	495	99.0	8.73
Monitored in the emergency department	491	98.2	5.55
QTc>500ms	478	95.6	10.07
Radiates to jaw or arm	468	93.6	2.93
Family history of CAD	366	73.2	3.14
Systolic blood pressure <90 or >160 mmHg	359	71.8	2.41
Symptoms relieved by nitroglycerin	285	57.0	2.70
Active smoker	250	50.0	1.97
Age >65	161	32.2	
Crushing chest pain	147	29.4	
Vasculopathy (1 out of 4 of CAD, TIA, PVD or stroke)	92	18.4	
Heart rate <60 or >100 beats per minute	80	16.0	
Metabolic disease (2 of 3 of hypertension, hypercholesterolemia or diabetes)	67	13.4	

Table 13. Variables in the derived abnormal troponin logistic regression model.

Variable	**OR (95% Wald Confidence Limits)**
Age>60	5.18 (3.34, 8.02)
Male	2.38 (1.57, 3.59)
Arrival by ambulance	1.77 (1.16, 2.72)
Monitored in the emergency department	2.47 (1.61, 3.80)
Known congestive heart failure	6.78 (3.13, 14.68)
Known renal failure	6.47 (2.31, 18.11)
Taking a cholesterol lowering medication	2.05 (1.37, 3.08)
Exertional chest pain	1.79 (1.07, 3.00)
Pain radiating to the arm or jaw	1.64 (1.04, 2.58)
Final electrocardiogram interpretation suggestive of infarction or ischemia not known to be old	5.67 (2.55, 12.59)
QTc>500ms	5.84 (1.90, 17.99)

Table 14. Analysis of maximum likelihood estimates in abnormal troponin logistic regression model.

Parameter	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept	-4.2500	0.2957	206.6015	<.0001
Age>60	1.6439	0.2234	54.1655	<.0001
Male	0.8649	0.2105	16.8877	<.0001
Arrival by ambulance	0.5723	0.2186	6.8555	0.0088
Monitored in the emergency department	0.9046	0.2195	16.9904	<.0001
Known congestive heart failure	1.9142	0.3942	23.5836	<.0001
Known renal failure	1.8671	0.5250	12.6464	0.0004
Taking a cholesterol lowering medication	0.7200	0.2069	12.1039	0.0005
Exertional chest pain	0.5813	0.2631	4.8809	0.0272
Pain radiating to the arm or jaw	0.4922	0.2331	4.4575	0.0347
Final electrocardiogram interpretation suggestive of infarction or ischemia not known to be old	1.7347	0.4072	18.1497	<.0001
QTc>500ms	1.7644	0.5742	9.4430	0.0021

Table 15. Frequency of variable selection during the 500 sample bootstrapping internal validation procedure of the abnormal troponin logistic regression model.

Variable	**Frequency**	**% of bootstraps**	**OR in Derived Model**
Age>60	500	100	5.18
Known congestive heart failure	499	99.8	6.78
Male	494	98.8	2.38
Monitored in the emergency department	494	98.8	2.47
Final electrocardiogram interpretation suggestive of infarction or ischemia not known to be old	483	96.6	5.67
Known renal failure	482	96.4	6.47
Taking a cholesterol-lowering medication	476	95.2	2.05
QTc>500ms	437	87.4	5.84
Arrival by ambulance	351	70.2	1.77
Pain radiating to the arm or jaw	333	66.6	1.64
Exertional pain or relieved by rest	281	56.2	1.79
Symptoms relived by nitroglycerin	189	37.8	
Crushing chest pain	143	28.6	
Active smoker	113	22.6	
Respiratory rate <12 or >20 breaths per minute	91	18.2	
Pulmonary embolism	82	16.4	
Family history of CAD	61	12.2	
Heart rate <60 or >100 beats per minute	61	12.2	
Systolic blood pressure <90 or >160 mmHg	52	10.4	
Atrial fibrillation or flutter	41	8.2	
Shortness of breath	38	7.6	
Metabolic disease (hypertension and diabetes)	36	7.2	

Table 16. Retained variables in the 8-variable machine learning major adverse cardiac events model with their respective impurity-based feature of importance.

Variable	**Impurity-based Importance**
Final electrocardiogram interpretation suggestive of infarction or ischemia not known to be old	0.2178
Presence of new ischemic changes on the second electrocardiogram done in the emergency department	0.1935
Age	0.1822
Systolic blood pressure	0.1529
Known obesity	0.0921
Known coronary artery disease	0.0714
Oxygen saturation	0.0709
New electrocardiogram t-wave changes	0.0192

Table 17. Retained variables in the 8-variable machine learning abnormal troponin model with their respective impurity-based feature of importance.

Variable	**Impurity-based Importance**
Age	0.3519
Final electrocardiogram interpretation as normal	0.1409
Not taking any medications	0.1217
Using a cholesterol-lowering medication	0.1180
History of renal failure	0.1046
History of congestive heart failure	0.0928
Known hypertension	0.0397
Abnormal electrocardiogram but not diagnostic of ischemia	0.0303

Table 18. Preliminary Chest Pain Risk Score.

Category	Points
Emergency Department Course	
Monitored in the emergency department	+3
Past Medical History	
Active smoker	+1
Family history of coronary artery disease	+2
Symptom Characteristics	
Exertional chest pain	+3
Pain radiating to the arm or jaw	+2
Symptoms relived by nitroglycerin	+2
Vital Signs	
Systolic blood pressure >160 or <90mmHg	+1
Electrocardiogram Characteristics	
Electrocardiogram suggestive of ischemia not known to be old	+3
QTc>500ms	+3
Total Score (0-20)	-

Total Score	Estimated Risk of MACE (%)	Risk Category
0-2	0.0%	Low
3-7	6.8%	Medium
8 or more	47.4%	High

Table 19. Clinical performance of the Preliminary Chest Pain Risk Score in identifying low risk chest pain patients from medium & high risk chest pain patients.

Statistic	**Value**	**95% CI**
Sensitivity	100.00%	94.87% to 100.00%
Specificity	47.67%	44.44% to 50.91%
Positive Likelihood Ratio	1.91	1.80 to 2.03
Negative Likelihood Ratio	0.00	-
Positive Predictive Value*	1.31%	1.23% to 1.39%
Negative Predictive Value*	100.00%	-
Accuracy	48.03%	44.92% to 51.16%

**The disease prevalence of 0.69% that we encountered in our study was used in the predictive value calculations.*

Table 20. Clinical performance of the Preliminary Chest Pain Risk Score in identifying high risk chest pain patients from low & medium risk chest pain patients.

Statistic	**Value**	**95% CI**
Sensitivity	52.86%	40.55% to 64.91%
Specificity	95.66%	94.15% to 96.87%
Positive Likelihood Ratio	12.17	8.39 to 17.66
Negative Likelihood Ratio	0.49	0.38 to 0.63
Positive Predictive Value*	7.80%	5.51% to 10.93%
Negative Predictive Value*	99.66%	99.56% to 99.73%
Accuracy	95.36%	93.88% to 96.57%

**The disease prevalence of 0.69% that we encountered in our study was used in the predictive value calculations.*

Table 21. Ultra-Low Risk Troponin Score.

Category	**Points**
Demographics	
Age>60	+3
Male	+2
Past Medical History	
Known congestive heart failure	+4
Known renal failure	+4
Taking a cholesterol-lowering medication	+1
Symptom Characteristics	
Exertional chest pain	+1
Pain radiating to the arm or jaw	+1
Initial Emergency Department Course	
Arrival by ambulance	+1
Monitored in the emergency department	+2
Electrocardiogram Characteristics	
Electrocardiogram suggestive of ischemia not known to be old	+4
QTc>500ms	+4
Total Score (0-27)	-

Total Score	**Estimated Risk of an Abnormal Troponin (%)**	**Risk Category**
0	0.00	Ultra-Low
1-2	2.7	Low
3-5	9.7	Medium
6-11	43.9	High
12 or more	91.0	Very High

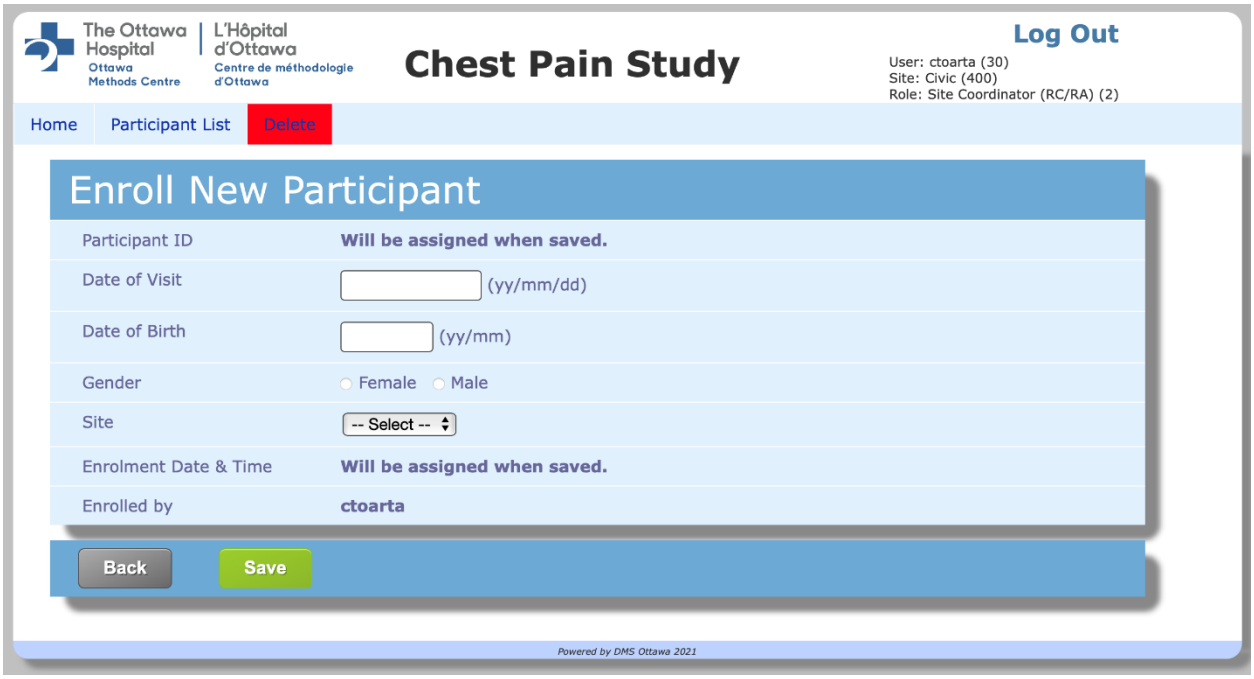
Table 22. Clinical performance of the Ultra-Low Risk Troponin Score in identifying ultra-low risk chest pain patients from those in other risk categories.

Statistic	**Value**	**95% CI**
Sensitivity	100.00%	98.38% to 100.00%
Specificity	14.07%	11.65% to 16.79%
Positive Likelihood Ratio	1.16	1.13 to 1.20
Negative Likelihood Ratio	0.00	-
Positive Predictive Value*	26.23%	25.67% to 26.80%
Negative Predictive Value*	100.00%	-
Accuracy	34.18%	31.19% to 37.27%

**The disease prevalence of 23.4%, representing the proportion of patients with an abnormal troponin test in our study, was used in the predictive value calculations.*

APPENDICES

Appendix 1. Digital case collection form.



Visit History

Arrived by Ambulance	Yes	No				
Was patient monitored in ED	Yes	No				
Time of Registration	(hh:mm)	Not documented (ND)				
Time of arrival to bed/treatment area	(hh:mm)	ND	+1 day	Date	(mm/dd)	
Time of initial assessment by physician	(hh:mm)	ND	+1 day	Date	(mm/dd)	
Time of discharge / referral	(hh:mm)	ND	+1 day	Date	(mm/dd)	

Medical History

Smoking history	Current smoker	Previous smoker	None	NA
Known coronary artery disease	Yes	No	NA	
Family history of coronary artery disease	Yes	No	NA	
Hypertension	Yes	No	NA	
Diabetes	Yes	No	NA	
Hypercholesterolemia / Hyperlipidemia	Yes	No	NA	
TIA	Yes	No	NA	
CVA	Yes	No	NA	
Obesity (BMI > 30kg/m^2)	Yes	No	NA	
Peripheral vascular disease	Yes	No	NA	
Known congestive heart failure	Yes	No	NA	
ICD / Pacemaker	Yes	No	NA	
Known COPD	Yes	No	NA	
Renal Failure	Yes	No	NA	
Ventricular arrhythmia	Yes	No	NA	
Atrial Fib / Flutter	Yes	No	NA	
Cardiac Arrest	Yes	No	NA	
Pulmonary Embolism	Yes	No	NA	
Angina	Yes	No	NA	

Vitals

Temperature	(C)
Heart rate	(BPM)
Repiratory rate	
SBP	(mmHg)
DBP	(mmHg)
SaO2	(%) ○ Room air ○ Supplement O2

Medications

- ☐ Aspirin
- ☐ Plavix (clopidogrel)
- ☐ Beta blockers (e.g. metoprolol, atenolol)
- ☐ Calcium channel blockers (e.g.,diltiazem, verapamil)
- ☐ Nitroglycerin (or other nitrates)
- ☐ ACE-inhibitors
- ☐ Other anticoagulants (e.g., Coumadin, Aggrenox, newer oral anticoagulants)
- ☐ Cholesterol-lowering drug
- ☐ None of the above

Troponin

Type of assay ○ Conventional Troponin ○ High-sensitive Troponin

	Date (yy/mm/dd)	Time (hh:mm)	Conventional tni ≤ 45 ng/L	High-sensitive tni ≤ 14 ng/L	If No, Value	Not Available
1st Troponin			○ Yes ○ No	○ Yes ○ No		☐ NA
2nd Troponin			○ Yes ○ No	○ Yes ○ No		☐ NA
3rd Troponin			○ Yes ○ No	○ Yes ○ No		☐ NA
Highest Troponin			○ Yes ○ No	○ Yes ○ No		☐ NA

History of Presenting Illness (Physician's Note)

Crushing chest pain	○ Yes ○ No ○ NA
Exertional pain/ Relieved by rest	○ Yes ○ No ○ NA
Pain radiates to the jaw or arm	○ Yes ○ No ○ NA
Single episode	○ Yes ○ No ○ NA
Ongoing symptoms	○ Yes ○ No ○ NA
Symptoms relieved by nitro spray	○ Yes ○ No ○ NA
Middle or left sided chest pain	○ Yes ○ No ○ NA
Other associated symptoms	☐ Shortness of breath ☐ Diaphoresis ☐ GI symptoms (nausea or vomiting)

Symptoms/ symptom characteristics associated with other entities

Cough	○ Yes ○ No ○ NA
Fever	○ Yes ○ No ○ NA
Pleuritic Chest Pain	○ Yes ○ No ○ NA
Positional Chest Pain	○ Yes ○ No ○ NA
Tearing Chest Pain	○ Yes ○ No ○ NA

ECG

ED ECG	○ Done ○ Not done If Yes, How many [ ]
Previous Last ECG	Date [ ] (yy/mm/dd) Time [ ] (hh:mm) ☐ NA
ED ECG # 1	Date [ ] (yy/mm/dd) Time [ ] (hh:mm)
Rate	[ ]
PR interval	[ ]
QRS duration	[ ]
QRS axis	[ ]
QTc	[ ]
Rhythm	○ Sinus ○ Non-sinus ○ Sinus arrhythmia
If Non-sinus or Sinus arrhythmia, Is it new?	○ Yes ○ No ○ Unknown
If Non-sinus, Specify	-- Select -- If Other, Specify [ ]
Morphology	☐ ST-segment depression ☐ T-wave inversion ☐ Left bundle branch block ☐ Right bundle branch block ☐ Pathological Q waves
If ST-segment depression	○ < ½ mm in at least 2 contiguous leads ○ ½ to 1 mm in at least 2 contiguous leads ○ > 1mm in at least 2 contiguous leads If Yes, Indicate if new ○ Yes ○ No ○ Unknown
If T-wave inversion	○ > 0.2 mm in 2/more contiguous leads with dominant R waves ○ < 0.2 mm in 2/more contiguous leads with dominant R waves If Yes, Indicate if new ○ Yes ○ No ○ Unknown
If Left bundle branch block	If Yes, Indicate if new ○ Yes ○ No ○ Unknown
If Right bundle branch block	If Yes, Indicate if new ○ Yes ○ No ○ Unknown
If Pathological Q waves	If Yes, Indicate if new ○ Yes ○ No ○ Unknown
Overall interpretation	-- Select --

Outcome Assessment

Index ED Visit Outcome Assessment

Index ED Visit Date	[ ] (yy/mm/dd)
Outcomes during Index ED Visit	○ Yes ○ No
Cardiac Death	○ Yes ○ No If Yes, Date [ ] (yy/mm/dd)
Death from unknown cause	○ Yes ○ No If Yes, Date [ ] (yy/mm/dd)
Cardiac Arrest	○ Yes ○ No If Yes, Date [ ] (yy/mm/dd)
ST-elevation myocardial infarction (STEMI)	○ Yes ○ No If Yes, Date [ ] (yy/mm/dd)
Non-STEMI	○ Yes ○ No If Yes, Date [ ] (yy/mm/dd)
Unstable Angina	○ Yes ○ No If Yes, Date [ ] (yy/mm/dd)
Revascularization Procedure	○ Yes ○ No If Yes, Date [ ] (yy/mm/dd) Specify ○ Emergent ○ Urgent Type ○ Stent ○ CABG
Heart Failure Requiring Intervention	○ Yes ○ No If Yes, Date [ ] (yy/mm/dd)
Cardiogenic Shock	○ Yes ○ No If Yes, Date [ ] (yy/mm/dd)
High-Degree Atrioventricular Block	○ Yes ○ No If Yes, Date [ ] (yy/mm/dd)
Ventricular Arrhythmia	○ Yes ○ No If Yes, Date [ ] (yy/mm/dd)
Primary Event	-- Select -- If Other, Specify [ ]
When did it occur or when was it detected?	[ ] (yy/mm/dd) Time [ ] (hh:mm) ☐ NA
Where did it occur or where was it detected?	○ In the ED before disposition decision (includes those detected in the prehospital setting) ○ Outside the ED If Outside the ED, Specify where ○ In ED after disposition decision ○ As Inpatient ○ After index visit (home or outpatient) Was the event expected or suspected during the ED visit? ○ Yes ○ No

Appendix 2. Summary of the variables collected.

	Demographics	Type of Variable
1	Age (years)[†]	Continuous
2	Male sex	Dichotomous
	Initial ED course	
3	Arrival by ambulance	Dichotomous
4	Monitored in the emergency department	Dichotomous
	Past Medical History	
5	Smoking status (none, prior smoker, active smoker) [†]*	Categorical
6	Known coronary artery disease	Dichotomous
7	Angina	Dichotomous
8	Family history of coronary artery disease	Dichotomous
9	Chronic obstructive pulmonary disease	Dichotomous
10	Hypertension	Dichotomous
11	Diabetes	Dichotomous
12	Hypercholesterolemia	Dichotomous
13	Transient ischemic attack	Dichotomous
14	Cerebrovascular accident	Dichotomous
15	Obesity	Dichotomous
16	Peripheral vascular disease	Dichotomous
17	Congestive heart failure	Dichotomous
18	Implantable cardioverter-defibrillator/Pacemaker	Dichotomous
19	Renal failure	Dichotomous
20	Ventricular arrhythmia	Dichotomous
21	Atrial fibrillation/flutter	Dichotomous
22	Cardiac arrest	Dichotomous
23	Pulmonary embolism	Dichotomous
	Medications	
24	Aspirin	Dichotomous
25	Clopidogrel or ticagrelor	Dichotomous
26	Other anticoagulants	Dichotomous
27	Beta blockers	Dichotomous
28	Calcium channel blockers	Dichotomous
29	Nitroglycerin or other nitrates	Dichotomous
30	ACE inhibitors/Angiotensin receptor blockers	Dichotomous
31	Cholesterol-lowering medications	Dichotomous
32	None of the above	Dichotomous
	History of Presenting Illness	
33	Crushing/Pressure	Dichotomous
34	Exertional or relieved by rest	Dichotomous
35	Radiates to jaw or arm	Dichotomous
36	Single episode	Dichotomous
37	Ongoing symptoms	Dichotomous

38	Relieved by nitroglycerin	Dichotomous
39	Middle or left sided	Dichotomous
40	Pleuritic	Dichotomous
41	Positional*	Dichotomous
42	Tearing	Dichotomous
43	Shortness of breath	Dichotomous
44	Diaphoresis	Dichotomous
45	Gastrointestinal symptoms (nausea or vomiting)	Dichotomous
46	Cough	Dichotomous
47	Fever	Dichotomous
	Vital Signs	
48	Heart rate (beats per minute)	Continuous
49	Respiratory rate (breaths per minute) †	Continuous
50	Systolic blood pressure (mmHg) †	Continuous
51	Diastolic blood pressure (mmHg) †	Continuous
52	Temperature (°C) †	Continuous
53	Oxygen saturation (%O2) †	Continuous
54	Use of supplemental oxygen	Dichotomous
	Electrocardiogram Characteristics	
55	Rhythm (sinus, supra-ventricular tachycardia, multifocal atrial tachycardia, atrial flutter, atrial fibrillation, ventricular tachycardia, ventricular fibrillation, junctional rhythm, idioventricular rhythm, paced rhythm, other)	Categorical
56	If non sinus: old or not*	Dichotomous
57	ECG morphology (ST-segment depression, T-wave inversion, left bundle branch block, right bundle branch block, pathological Q waves)*	Categorical
58	If ST depressions: Less than ½ mm in at least 2 contiguous leads, ½ to 1 mm in at least 2 contiguous leads, greater than 1mm in at least 2 contiguous leads*	Categorical
59	If ST depressions: old or not	Dichotomous
60	If T wave inversions: greater than 0.2 mm in 2/more contiguous leads with dominant R waves or less than 0.2 mm in 2/more contiguous leads with dominant R waves*	Categorical
61	If T-wave inversion: old or not	Dichotomous
62	If left bundle branch block: old or not*	Dichotomous
63	If right bundle branch block: old or not	Dichotomous
64	If pathological q wave: old or not*	Dichotomous
65	Electrocardiogram heart rate (bpm)*	Continuous
66	PR interval (ms)*	Continuous
67	QRS axis (°)*	Continuous
68	QRS interval (ms)*	Continuous
69	QTc interval (ms) †*	Continuous
70	Final electrocardiogram interpretation (normal, nonspecific ST-T wave changes, normal but not diagnostic of ischemia, infarction or	Categorical

	ischemia known to be old, infarction or ischemia not known to be old, uninterpretable) †	
71	Presence of new ischemic changes on the second electrocardiogram done in the emergency department: yes or no	Dichotomous

† *Predictor variables that were transformed from either continuous or categorical variables into dichotomous variables for the logistic regression multivariable analysis and clinical decision scores derivation.*

**Predictor variables that were not used for the machine learning modelling.*

Appendix 3. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) checklist.

TRIPOD Checklist: Prediction Model Development

Section/Topic	Item	Checklist Item	Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	Cover
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	i
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	22
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	23, 24
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	25
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	25
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	25
	5b	Describe eligibility criteria for participants.	25, 26
	5c	Give details of treatments received, if relevant.	Not Applicable
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	33
	6b	Report any actions to blind assessment of the outcome to be predicted.	-
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	27-32
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	-
Sample size	8	Explain how the study size was arrived at.	26, 27
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	34, 35, 44
Statistical analysis methods	10a	Describe how predictors were handled in the analyses.	27-32, 44-51
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	32, 37, 38
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	38, 39
Risk groups	11	Provide details on how risk groups were created, if done.	39, 40
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	74
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	81-89
Model development	14a	Specify the number of participants and outcome events in each analysis.	44, 47
	14b	If done, report the unadjusted association between each candidate predictor and outcome.	Not Applicable
Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	91, 95
	15b	Explain how to the use the prediction model.	60-62
Model performance	16	Report performance measures (with CIs) for the prediction model.	92
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	64-66
Interpretation	19b	Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.	52-66
Implications	20	Discuss the potential clinical use of the model and implications for future research.	67
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	104
Funding	22	Give the source of funding and the role of the funders for the present study.	v

Appendix 4. Pearson correlation coefficient matrix for variables used in the derivation of the major adverse cardiac events logistic regression model.

Pearson Correlation Coefficients, N = 1014														
Prob > |r| under H0: Rho=0														
	a	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**	**j**	**k**	**l**	**m**	**n**
a	1.0000	0.3674	0.2046	-0.0541	0.3824	0.1426	0.0758	0.1267	-0.0538	0.1612	0.0208	0.2169	0.1504	0.1305
		<.0001	<.0001	0.0851	<.0001	<.0001	0.0157	<.0001	0.0866	<.0001	0.5074	<.0001	<.0001	<.0001
b	0.3674	1.0000	0.1560	0.0137	0.4178	0.1089	0.1182	0.1384	0.0658	0.2388	0.1254	0.1026	0.1449	0.1112
	<.0001		<.0001	0.6624	<.0001	0.0005	0.0002	<.0001	0.0360	<.0001	<.0001	0.0011	<.0001	0.0004
c	0.2046	0.1560	1.0000	0.0549	0.2228	0.0147	0.0599	0.1510	0.0206	0.0618	0.0934	0.0569	0.0535	0.0130
	<.0001	<.0001		0.0806	<.0001	0.6398	0.0568	<.0001	0.5121	0.0493	0.0029	0.0700	0.0889	0.6794
d	-0.0541	0.0137	0.0549	1.0000	-0.0200	-0.0277	0.1174	-0.0239	0.0403	0.0222	0.0078	0.0324	0.0356	-0.0510
	0.0851	0.6624	0.0806		0.5248	0.3780	0.0002	0.4469	0.1997	0.4793	0.8049	0.3032	0.2570	0.1047
e	0.3824	0.4178	0.2228	-0.0200	1.0000	0.0844	0.0200	0.1231	-0.0351	0.2315	0.0289	0.0579	0.0794	0.0883
	<.0001	<.0001	<.0001	0.5248		0.0072	0.5248	<.0001	0.2638	<.0001	0.3578	0.0654	0.0114	0.0049
f	0.1426	0.1089	0.0147	-0.0277	0.0844	1.0000	-0.0036	-0.0188	0.0372	0.0301	0.0968	0.0432	0.0530	0.0283
	<.0001	0.0005	0.6398	0.3780	0.0072		0.9092	0.5495	0.2362	0.3378	0.0020	0.1695	0.0916	0.3689
g	0.0758	0.1182	0.0599	0.1174	0.0200	-0.0036	1.0000	0.1515	0.0435	0.0947	0.0354	0.0431	0.0777	-0.0457
	0.0157	0.0002	0.0568	0.0002	0.5248	0.9092		<.0001	0.1665	0.0025	0.2607	0.1701	0.0134	0.1459
h	0.1267	0.1384	0.1510	-0.0239	0.1231	-0.0188	0.1515	1.0000	0.0680	0.0968	0.0469	0.0134	0.0749	-0.0268
	<.0001	<.0001	<.0001	0.4469	<.0001	0.5495	<.0001		0.0303	0.0020	0.1355	0.6699	0.0170	0.3943
i	-0.0538	0.0658	0.0206	0.0403	-0.0351	0.0372	0.0435	0.0680	1.0000	0.0756	-0.0154	-0.0195	0.0361	-0.0642
	0.0866	0.0360	0.5121	0.1997	0.2638	0.2362	0.1665	0.0303		0.0160	0.6251	0.5344	0.2510	0.0411
j	0.1612	0.2388	0.0618	0.0222	0.2315	0.0301	0.0947	0.0968	0.0756	1.0000	-0.0164	-0.0183	-0.0158	-0.0426
	<.0001	<.0001	0.0493	0.4793	<.0001	0.3378	0.0025	0.0020	0.0160		0.6013	0.5609	0.6155	0.1756
k	0.0208	0.1254	0.0934	0.0078	0.0289	0.0968	0.0354	0.0469	-0.0154	-0.0164	1.0000	0.0087	0.0835	0.0008
	0.5074	<.0001	0.0029	0.8049	0.3578	0.0020	0.2607	0.1355	0.6251	0.6013		0.7817	0.0078	0.9810
l	0.2169	0.1026	0.0569	0.0324	0.0579	0.0432	0.0431	0.0134	-0.0195	-0.0183	0.0087	1.0000	0.0567	0.0310
	<.0001	0.0011	0.0700	0.3032	0.0654	0.1695	0.1701	0.6699	0.5344	0.5609	0.7817		0.0710	0.3249
m	0.1504	0.1449	0.0535	0.0356	0.0794	0.0530	0.0777	0.0749	0.0361	-0.0158	0.0835	0.0567	1.0000	0.0239
	<.0001	<.0001	0.0889	0.2570	0.0114	0.0916	0.0134	0.0170	0.2510	0.6155	0.0078	0.0710		0.4481
n	0.1305	0.1112	0.0130	-0.0510	0.0883	0.0283	-0.0457	-0.0268	-0.0642	-0.0426	0.0008	0.0310	0.0239	1.0000
	<.0001	0.0004	0.6794	0.1047	0.0049	0.3689	0.1459	0.3943	0.0411	0.1756	0.9810	0.3249	0.4481	

a=Age>65, b=Monitored in the ED, c=Active smoker, d=Family history of coronary artery disease, e=Vasculopathy (at least 1 out of 4 of the following: coronary artery disease or transient ischemic attack or stroke or peripheral vascular disease), f=Metabolic disease (at least 2 out of 3 of the following: hypertension or hypercholesterolemia or diabetes), g= Crushing/pressure, h= Exertional or relieved by rest, i= Radiates to jaw, j=Relieved by nitroglycerin, k= Heart rate <60 or >100 beats per minute, l=Systolic blood pressure <90 or >160 mmHg, m= Final electrocardiogram interpretation suggestive of infarction or ischemia not known to be old, n= QTc >500ms

Appendix 5. Tolerance and variance inflation for variables used in the derivation of the major adverse cardiac events logistic regression model.

Variable	Degrees of Freedom	Parameter Estimate	Standard Error	t Value	Pr > |t|	Tolerance	Variance Inflation
Intercept	1	-0.0441	0.0122	-3.61	0.0003	.	0
Age >65	1	0.0164	0.0172	0.96	0.3392	0.7254	1.3785
Monitored in the emergency department	1	0.049	0.017	2.89	0.0039	0.719	1.3908
Active smoker	1	0.0329	0.0191	1.73	0.0848	0.9076	1.1019
Family history of coronary artery disease	1	0.0627	0.0258	2.43	0.0152	0.9698	1.0311
Vasculopathy (at least 1 out of 4 of the following: coronary artery disease or transient ischemic attack or stroke or peripheral vascular disease)	1	0.0031	0.0187	0.17	0.8686	0.7283	1.3731
Metabolic disease (at least 2 out of 3 of the following: hypertension or hypercholesterolemia or diabetes)	1	0.0332	0.037	0.9	0.3702	0.9618	1.0397
Crushing/pressure	1	0.0247	0.0176	1.4	0.1612	0.94	1.0638
Exertional or relieved by rest	1	0.1398	0.0222	6.3	<.0001	0.9285	1.077
Radiates to jaw or arm	1	0.0598	0.017	3.51	0.0005	0.9673	1.0339
Relieved by nitroglycerin	1	0.0898	0.0313	2.87	0.0042	0.8947	1.1177
Heart rate <60 or >100 beats per minute	1	0.0094	0.0189	0.5	0.618	0.9601	1.0416
Systolic blood pressure <90 or >160 mmHg	1	0.0447	0.0189	2.36	0.0182	0.9446	1.0587
Final electrocardiogram interpretation suggestive of infarction or ischemia not known to be old	1	0.2812	0.0356	7.9	<.0001	0.9514	1.0511
QTc >500ms	1	0.1894	0.0453	4.18	<.0001	0.9618	1.0397

Appendix 6. Eigenvalues for variables used in the derivation of the major adverse cardiac events logistic regression model.

Collinearity Diagnostics																
	Eigen-	Condition	Proportion of Variation													
Number	value	Index	+	a	b	c	d	e	f	g	h	i	j	k	l	m	n
1	4.7261	1	0.0111	0.0121	0.0122	0.0113	0.0043	0.0119	0.0036	0.0105	0.0088	0.0087	0.006	0.0087	0.0092	0.0046	0.0019
2	1.1459	2.0309	0.0011	0.0185	0.0032	0.0004	0.1556	0.0175	0.0765	0.0623	0.0238	0.0524	0.0108	0.0000	0.0054	0.0028	0.2974
3	1.0511	2.1205	0.0024	0.0027	0.0038	0.0021	0.0841	0.0389	0.0281	0.0040	0.0264	0.0023	0.3306	0.0671	0.0390	0.1336	0.0075
4	0.9648	2.2133	0.0003	0.0007	0.0000	0.0159	0.0306	0.0005	0.5655	0.0052	0.0100	0.0198	0.0287	0.0331	0.0161	0.0008	0.2054
5	0.9276	2.2573	0.0039	0.0000	0.0001	0.0064	0.2138	0.0000	0.0377	0.0003	0.1891	0.0080	0.0133	0.0086	0.0307	0.3767	0.0462
6	0.8621	2.3414	0.0048	0.0023	0.0020	0.0572	0.1098	0.0061	0.0003	0.0002	0.0871	0.0099	0.1389	0.1417	0.0015	0.4101	0.0014
7	0.8291	2.3875	0.0006	0.0233	0.0004	0.0229	0.0063	0.0085	0.0019	0.0106	0.0148	0.123	0.0126	0.0359	0.3827	0.0019	0.3119
8	0.8092	2.4167	0.0035	0.0004	0.0003	0.1405	0.1268	0.0245	0.0012	0.0229	0.0229	0.2485	0.0052	0.1979	0.1340	0.0000	0.0099
9	0.7463	2.5165	0.0055	0.0003	0.0064	0.0005	0.0611	0.0023	0.2331	0.1462	0.2693	0.1694	0.0154	0.1209	0.0049	0.0164	0.0186
10	0.7329	2.5394	0.0002	0.0002	0.0015	0.2684	0.0325	0.0127	0.0261	0.2001	0.0041	0.1395	0.0774	0.2225	0.0389	0.0059	0.0019
11	0.6358	2.7264	0.0018	0.0037	0.0008	0.0915	0.1238	0.0044	0.0004	0.4349	0.3381	0.0002	0.0571	0.0484	0.0983	0.0005	0.0089
12	0.5863	2.8393	0.0093	0.0226	0.0523	0.3633	0.0181	0.1859	0.0134	0.0097	0.0048	0.002	0.2830	0.0054	0.1066	0.0262	0.0739
13	0.382	3.5174	0.0427	0.5520	0.0017	0.0012	0.0019	0.5039	0.0079	0.0429	0.0007	0.0159	0.0021	0.0042	0.1210	0.0050	0.0115
14	0.329	3.7899	0.0037	0.2099	0.8040	0.0170	0.0052	0.1810	0.0016	0.0139	0.0000	0.0526	0.0041	0.0516	0.0009	0.0003	0.0034
15	0.2718	4.1697	0.9091	0.1512	0.1115	0.0015	0.0262	0.0019	0.0030	0.0363	0.0004	0.1477	0.0150	0.0540	0.0108	0.0152	0.0003

+=Intercept, a=Age>65, b=Monitored in the ED, c=Active smoker, d=Family history of coronary artery disease, e=Vasculopathy (at least 1 out of 4 of the following: coronary artery disease or transient ischemic attack or stroke or peripheral vascular disease), f=Metabolic disease (at least 2 out of 3 of the following: hypertension or hypercholesterolemia or diabetes), g= Crushing/pressure, h= Exertional or relieved by rest, i= Radiates to jaw or arm, j=Relieved by nitroglycerin, k= Heart rate <60 or >100 beats per minute, l=Systolic blood pressure <90 or >160 mmHg, m= Final electrocardiogram interpretation suggestive of infarction or ischemia not known to be old, n= QTc >500ms

Appendix 7. Pearson correlation coefficient matrix for variables used in the derivation of the abnormal troponin LR model.

Pearson Correlation Coefficients, N = 965																						
Prob > |r| under H0: Rho=0																						
	a	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**	**j**	**k**	**l**	**m**	**n**	**o**	**p**	**q**	**r**	**s**	**t**	**u**	**v**
a	1.0000	0.0110	0.1969	0.3674	0.2046	-0.0541	0.3089	0.1983	0.2421	0.2274	0.0391	0.3911	0.0758	0.1267	-0.0538	0.1612	0.0523	0.0208	0.2169	0.0344	0.1504	0.1305
		0.7266	<.0001	<.0001	<.0001	0.0851	<.0001	<.0001	<.0001	<.0001	0.2134	<.0001	0.0157	<.0001	0.0866	<.0001	0.0958	0.5074	<.0001	0.2741	<.0001	<.0001
b	0.0110	1.0000	-0.0200	0.1068	0.1201	0.0043	0.0587	0.0324	0.0879	0.0764	-0.0115	0.1512	0.0112	0.0646	-0.0709	0.0614	-0.0208	0.0411	-0.0633	0.0106	0.0267	0.0499
	0.7266		0.5239	0.0007	0.0001	0.8916	0.0617	0.3030	0.0051	0.0149	0.7141	<.0001	0.7224	0.0396	0.0240	0.0508	0.5091	0.1907	0.0440	0.7351	0.3951	0.1120
c	0.1969	-0.0200	1.0000	0.2240	0.0735	-0.0254	0.0968	0.1773	0.1330	0.1582	0.0806	0.1795	0.0380	-0.0494	-0.0229	0.1809	0.0235	-0.0094	0.0161	0.0559	0.0585	0.0937
	<.0001	0.5239		<.0001	0.0193	0.4201	0.0020	<.0001	<.0001	<.0001	0.0103	<.0001	0.2271	0.1157	0.4661	<.0001	0.4548	0.7651	0.6095	0.0751	0.0625	0.0028
d	0.3674	0.1068	0.2240	1.0000	0.1560	0.0137	0.2544	0.2008	0.1487	0.2140	0.0652	0.3468	0.1182	0.1384	0.0658	0.2388	0.1263	0.1254	0.1026	0.1532	0.1449	0.1112
	<.0001	0.0007	<.0001		<.0001	0.6624	<.0001	<.0001	<.0001	<.0001	0.0378	<.0001	0.0002	<.0001	0.0360	<.0001	<.0001	<.0001	0.0011	<.0001	<.0001	0.0004
e	0.2046	0.1201	0.0735	0.1560	1.0000	0.0549	0.0891	0.1418	0.0747	0.1358	0.0349	0.1773	0.0599	0.1510	0.0206	0.0618	0.0680	0.0934	0.0569	0.0122	0.0535	0.0130
	<.0001	0.0001	0.0193	<.0001		0.0806	0.0045	<.0001	0.0174	<.0001	0.2669	<.0001	0.0568	<.0001	0.5121	0.0493	0.0303	0.0029	0.0700	0.6978	0.0889	0.6794
f	-0.0541	0.0043	-0.0254	0.0137	0.0549	1.0000	-0.0213	-0.0800	-0.0672	-0.0545	-0.0448	-0.0119	0.1174	-0.0239	0.0403	0.0222	-0.0195	0.0078	0.0324	-0.0486	0.0356	-0.0510
	0.0851	0.8916	0.4201	0.6624	0.0806		0.4988	0.0108	0.0324	0.0827	0.1537	0.7056	0.0002	0.4469	0.1997	0.4793	0.5349	0.8049	0.3032	0.1220	0.2570	0.1047
g	0.3089	0.0587	0.0968	0.2544	0.0891	-0.0213	1.0000	0.1350	0.1027	0.1483	0.0522	0.2500	0.0110	0.0665	-0.0230	0.1385	0.0660	-0.0349	0.1263	0.0560	0.0959	0.1206
	<.0001	0.0617	0.0020	<.0001	0.0045	0.4988		<.0001	0.0011	<.0001	0.0964	<.0001	0.7258	0.0342	0.4637	<.0001	0.0358	0.2667	<.0001	0.0748	0.0022	0.0001
h	0.1983	0.0324	0.1773	0.2008	0.1418	-0.0800	0.1350	1.0000	0.3722	0.3781	0.1046	0.2181	0.1015	0.0339	-0.0032	0.0508	0.1121	0.0656	-0.0097	0.0592	0.0622	0.1838
	<.0001	0.3030	<.0001	<.0001	<.0001	0.0108	<.0001		<.0001	<.0001	0.0008	<.0001	0.0012	0.2808	0.9188	0.1059	0.0003	0.0367	0.7583	0.0595	0.0476	<.0001
i	0.2421	0.0879	0.1330	0.1487	0.0747	-0.0672	0.1027	0.3722	1.0000	0.1752	0.1014	0.2387	0.0630	0.0723	-0.0003	0.0813	0.0838	0.0191	0.0174	0.1291	0.0911	0.0817
	<.0001	0.0051	<.0001	<.0001	0.0174	0.0324	0.0011	<.0001		<.0001	0.0012	<.0001	0.0449	0.0213	0.9933	0.0096	0.0076	0.5429	0.5810	<.0001	0.0037	0.0093
j	0.2274	0.0764	0.1582	0.2140	0.1358	-0.0545	0.1483	0.3781	0.1752	1.0000	0.0568	0.2311	0.0337	0.0346	-0.0179	0.1153	0.0596	0.1441	-0.0244	0.0047	0.0742	0.1059
	<.0001	0.0149	<.0001	<.0001	<.0001	0.0827	<.0001	<.0001	<.0001		0.0707	<.0001	0.2834	0.2713	0.5701	0.0002	0.0577	<.0001	0.4375	0.8807	0.0181	0.0007
k	0.0391	-0.0115	0.0806	0.0652	0.0349	-0.0448	0.0522	0.1046	0.1014	0.0568	1.0000	0.0703	0.0039	0.0064	0.0157	0.0200	0.0100	-0.0331	-0.0163	-0.0218	-0.0313	0.0190
	0.2134	0.7141	0.0103	0.0378	0.2669	0.1537	0.0964	0.0008	0.0012	0.0707		0.0251	0.9009	0.8394	0.6176	0.5258	0.7505	0.2918	0.6051	0.4875	0.3188	0.5464
l	0.3911	0.1512	0.1795	0.3468	0.1773	-0.0119	0.2500	0.2181	0.2387	0.2311	0.0703	1.0000	0.0184	0.1656	-0.0017	0.1779	0.0171	-0.0007	0.0550	0.0467	0.0774	0.1315
	<.0001	<.0001	<.0001	<.0001	<.0001	0.7056	<.0001	<.0001	<.0001	<.0001	0.0251		0.5578	<.0001	0.9577	<.0001	0.5862	0.9817	0.0802	0.1377	0.0137	<.0001
m	0.0758	0.0112	0.0380	0.1182	0.0599	0.1174	0.0110	0.1015	0.0630	0.0337	0.0039	0.0184	1.0000	0.1515	0.0435	0.0947	0.1056	0.0354	0.0431	0.0011	0.0777	-0.0457
	0.0157	0.7224	0.2271	0.0002	0.0568	0.0002	0.7258	0.0012	0.0449	0.2834	0.9009	0.5578		<.0001	0.1665	0.0025	0.0008	0.2607	0.1701	0.9725	0.0134	0.1459
n	0.1267	0.0646	-0.0494	0.1384	0.1510	-0.0239	0.0665	0.0339	0.0723	0.0346	0.0064	0.1656	0.1515	1.0000	0.0680	0.0968	0.1399	0.0469	0.0134	-0.0184	0.0749	-0.0268
	<.0001	0.0396	0.1157	<.0001	<.0001	0.4469	0.0342	0.2808	0.0213	0.2713	0.8394	<.0001	<.0001		0.0303	0.0020	<.0001	0.1355	0.6699	0.5577	0.0170	0.3943
o	-0.0538	-0.0709	-0.0229	0.0658	0.0206	0.0403	-0.0230	-0.0032	-0.0003	-0.0179	0.0157	-0.0017	0.0435	0.0680	1.0000	0.0756	-0.0117	-0.0154	-0.0195	-0.0486	0.0361	-0.0642
	0.0866	0.0240	0.4661	0.0360	0.5121	0.1997	0.4637	0.9188	0.9933	0.5701	0.6176	0.9577	0.1665	0.0303		0.0160	0.7090	0.6251	0.5344	0.1216	0.2510	0.0411
p	0.1612	0.0614	0.1809	0.2388	0.0618	0.0222	0.1385	0.0508	0.0813	0.1153	0.0200	0.1779	0.0947	0.0968	0.0756	1.0000	0.0266	-0.0164	-0.0183	0.0040	-0.0158	-0.0426
	<.0001	0.0508	<.0001	<.0001	0.0493	0.4793	<.0001	0.1059	0.0096	0.0002	0.5258	<.0001	0.0025	0.0020	0.0160		0.3976	0.6013	0.5609	0.8978	0.6155	0.1756
q	0.0523	-0.0208	0.0235	0.1263	0.0680	-0.0195	0.0660	0.1121	0.0838	0.0596	0.0100	0.0171	0.1056	0.1399	-0.0117	0.0266	1.0000	0.0215	-0.0333	0.1439	0.0253	0.0914
	0.0958	0.5091	0.4548	<.0001	0.0303	0.5349	0.0358	0.0003	0.0076	0.0577	0.7505	0.5862	0.0008	<.0001	0.7090	0.3976		0.4944	0.2895	<.0001	0.4219	0.0036
r	0.0208	0.0411	-0.0094	0.1254	0.0934	0.0078	-0.0349	0.0656	0.0191	0.1441	-0.0331	-0.0007	0.0354	0.0469	-0.0154	-0.0164	0.0215	1.0000	0.0087	0.0898	0.0835	0.0008
	0.5074	0.1907	0.7651	<.0001	0.0029	0.8049	0.2667	0.0367	0.5429	<.0001	0.2918	0.9817	0.2607	0.1355	0.6251	0.6013	0.4944		0.7817	0.0042	0.0078	0.9810
s	0.2169	-0.0633	0.0161	0.1026	0.0569	0.0324	0.1263	-0.0097	0.0174	-0.0244	-0.0163	0.0550	0.0431	0.0134	-0.0195	-0.0183	-0.0333	0.0087	1.0000	0.1221	0.0567	0.0310
	<.0001	0.0440	0.6095	0.0011	0.0700	0.3032	<.0001	0.7583	0.5810	0.4375	0.6051	0.0802	0.1701	0.6699	0.5344	0.5609	0.2895	0.7817		<.0001	0.0710	0.3249
t	0.0344	0.0106	0.0559	0.1532	0.0122	-0.0486	0.0560	0.0592	0.1291	0.0047	-0.0218	0.0467	0.0011	-0.0184	-0.0486	0.0040	0.1439	0.0898	0.1221	1.0000	0.0153	0.1184
	0.2741	0.7351	0.0751	<.0001	0.6978	0.1220	0.0748	0.0595	<.0001	0.8807	0.4875	0.1377	0.9725	0.5577	0.1216	0.8978	<.0001	0.0042	<.0001		0.6267	0.0002
u	0.1504	0.0267	0.0585	0.1449	0.0535	0.0356	0.0959	0.0622	0.0911	0.0742	-0.0313	0.0774	0.0777	0.0749	0.0361	-0.0158	0.0253	0.0835	0.0567	0.0153	1.0000	0.0239
	<.0001	0.3951	0.0625	<.0001	0.0889	0.2570	0.0022	0.0476	0.0037	0.0181	0.3188	0.0137	0.0134	0.0170	0.2510	0.6155	0.4219	0.0078	0.0710	0.6267		0.4481
v	0.1305	0.0499	0.0937	0.1112	0.0130	-0.0510	0.1206	0.1838	0.0817	0.1059	0.0190	0.1315	-0.0457	-0.0268	-0.0642	-0.0426	0.0914	0.0008	0.0310	0.1184	0.0239	1.0000
	<.0001	0.1120	0.0028	0.0004	0.6794	0.1047	0.0001	<.0001	0.0093	0.0007	0.5464	<.0001	0.1459	0.3943	0.0411	0.1756	0.0036	0.9810	0.3249	0.0002	0.4481	

a=Age >60, b=Male, c=Arrival by ambulance, d=Monitored in the emergency department, e=Active smoker, f=Family history of coronary artery disease, g=Metabolic disease (hypertension and diabetes), h=Congestive heart failure, i=Renal failure, j=Atrial fibrillation/flutter, k=Pulmonary embolism, l=Cholesterol-lowering medications, m=Crushing/pressure, n=Exertional chest pain, o=Pain radiating to the arm or jaw, p=Symptoms relived by nitroglycerin, q=Associated shortness of breath, r=Heart rate <60 or >100 beats per minute, s=Systolic blood pressure <90 or >160 mmHg, t=Respiratory rate <12 or >20 breaths per minute , u=Final electrocardiogram interpretation suggestive of infarction or ischemia not known to be old, v= QTc>500ms

Appendix 8. Tolerance and variance inflation for variables used in the derivation of the abnormal troponin logistic regression model.

Parameter Estimates							
Variable	**Degrees of Freedom**	**Parameter Estimate**	**Standard Error**	**t Value**	**Pr > |t|**	**Tolerance**	**Variance Inflation**
Intercept	**1**	-0.0783	0.0235	-3.3300	0.0009	.	0.0000
Age >60	**1**	0.2065	0.0266	7.7700	<.0001	0.6738	1.4841
Male	**1**	0.0855	0.0223	3.8400	0.0001	0.9313	1.0738
Arrival by ambulance	**1**	0.0649	0.0265	2.4500	0.0143	0.8794	1.1372
Monitored in the emergency department	**1**	0.0948	0.0254	3.7300	0.0002	0.7149	1.3988
Active smoker	**1**	0.0381	0.0284	1.3400	0.1807	0.9008	1.1101
Family history of coronary artery disease	**1**	0.0022	0.0381	0.0600	0.9542	0.9575	1.0444
Metabolic disease (hypertension and diabetes)	**1**	-0.0098	0.0258	-0.3800	0.7037	0.8538	1.1713
Congestive heart failure	**1**	0.2682	0.0510	5.2600	<.0001	0.7152	1.3983
Renal failure	**1**	0.2852	0.0564	5.0500	<.0001	0.7954	1.2573
Atrial fibrillation/flutter	**1**	0.0026	0.0431	0.0600	0.9526	0.7879	1.2691
Pulmonary embolism	**1**	-0.0143	0.0765	-0.1900	0.8514	0.9686	1.0324
Cholesterol-lowering medications	**1**	0.1067	0.0269	3.9700	<.0001	0.7342	1.3620
Crushing/pressure	**1**	0.0334	0.0261	1.2800	0.2011	0.9290	1.0765
Exertional chest pain	**1**	0.0783	0.0333	2.3500	0.0189	0.8964	1.1156
Pain radiating to the arm or jaw	**1**	0.0530	0.0253	2.0900	0.0366	0.9596	1.0421
Symptoms relived by nitroglycerin	**1**	-0.0589	0.0462	-1.2700	0.2027	0.8819	1.1339
Associated shortness of breath	**1**	-0.0051	0.0242	-0.2100	0.8320	0.9226	1.0839
Heart rate <60 or >100 beats per minute	**1**	0.0186	0.0286	0.6500	0.5156	0.9350	1.0696
Systolic blood pressure <90 or >160 mmHg	**1**	0.0096	0.0287	0.3400	0.7367	0.9111	1.0976
Respiratory rate <12 or >20 breaths per minute	**1**	0.0278	0.0389	0.7100	0.4759	0.9069	1.1027
Final electrocardiogram interpretation suggestive of infarction or ischemia not known to be old	**1**	0.2481	0.0523	4.7400	<.0001	0.9449	1.0583
QTc>500ms	**1**	0.2848	0.0680	4.1900	<.0001	0.9149	1.0931

Appendix 9. Eigenvalues for variables used in the derivation of the abnormal troponin logistic regression model.

Number	Eigen-value	Condition Index	Proportion of Variation											
			+	a	b	c	d	e	f	g	h	i	j	k
1	6.8170	1.0000	0.0034	0.0052	0.0048	0.0050	0.0055	0.0049	0.0015	0.0055	0.0029	0.0025	0.0034	0.0008
2	1.5428	2.1021	0.0046	0.0011	0.0046	0.0052	0.0001	0.0015	0.0736	0.0004	0.0984	0.0766	0.0568	0.0204
3	1.1504	2.4342	0.0004	0.0000	0.0002	0.0025	0.0000	0.0047	0.0010	0.0013	0.0035	0.0028	0.0145	0.0639
4	1.0435	2.5559	0.0004	0.0041	0.0000	0.0290	0.0026	0.0120	0.0043	0.0311	0.0399	0.0150	0.0437	0.0783
5	0.9794	2.6383	0.0019	0.0203	0.0022	0.0074	0.0017	0.0009	0.0001	0.0289	0.0080	0.0101	0.0117	0.2962
6	0.9410	2.6916	0.0001	0.0023	0.0008	0.0016	0.0006	0.0005	0.1078	0.0042	0.0004	0.0002	0.0013	0.2838
7	0.9370	2.6972	0.0008	0.0071	0.0030	0.0319	0.0001	0.0005	0.2181	0.0081	0.0115	0.0457	0.0762	0.0200
8	0.8960	2.7582	0.0003	0.0023	0.0089	0.0252	0.0001	0.0679	0.0396	0.0109	0.0060	0.1548	0.0155	0.0018
9	0.8632	2.8103	0.0001	0.0008	0.0002	0.0063	0.0027	0.0090	0.1346	0.0000	0.0184	0.0340	0.0312	0.0603
10	0.8309	2.8644	0.0007	0.0085	0.0000	0.0291	0.0039	0.1006	0.0673	0.0000	0.0151	0.0607	0.0001	0.0281
11	0.7642	2.9866	0.0039	0.0002	0.0001	0.0017	0.0005	0.0152	0.0703	0.0000	0.0293	0.0050	0.0077	0.0881
12	0.7365	3.0423	0.0001	0.0016	0.0350	0.0036	0.0000	0.0880	0.0461	0.0019	0.0206	0.1099	0.0509	0.0022
13	0.6870	3.1500	0.0026	0.0009	0.0070	0.2469	0.0004	0.1492	0.0802	0.0056	0.0001	0.0084	0.0276	0.0357
14	0.6686	3.1931	0.0049	0.0008	0.0478	0.0513	0.0010	0.2540	0.0050	0.1808	0.0072	0.0063	0.0213	0.0016
15	0.6582	3.2183	0.0038	0.0038	0.0462	0.0564	0.0000	0.0901	0.0325	0.0348	0.0218	0.1108	0.1346	0.0047
16	0.5952	3.3844	0.0000	0.0004	0.0244	0.2562	0.0022	0.1323	0.0668	0.0668	0.0059	0.0104	0.0620	0.0012
17	0.5741	3.4460	0.0001	0.0036	0.0714	0.0202	0.0006	0.0002	0.0192	0.0016	0.0006	0.0563	0.0445	0.0011
18	0.5314	3.5816	0.0034	0.0006	0.1357	0.0326	0.0028	0.0036	0.0058	0.3634	0.0844	0.0175	0.1634	0.0053
19	0.4832	3.7560	0.0050	0.0972	0.2109	0.0249	0.0082	0.0180	0.0005	0.0133	0.3556	0.0516	0.0494	0.0001
20	0.4651	3.8283	0.0002	0.0120	0.0090	0.0826	0.0608	0.0233	0.0001	0.1776	0.2340	0.1584	0.1756	0.0001
21	0.3581	4.3634	0.0014	0.2567	0.0074	0.0260	0.3169	0.0038	0.0038	0.0427	0.0055	0.0000	0.0013	0.0000
22	0.3153	4.6499	0.0175	0.4844	0.0034	0.0004	0.5895	0.0171	0.0047	0.0112	0.0308	0.0475	0.0036	0.0043
23	0.1620	6.4878	0.9442	0.0861	0.3769	0.0542	0.0000	0.0026	0.0172	0.0097	0.0001	0.0152	0.0037	0.0019

Number	Eigen-value	Condition Index	Proportion of Variation										
			l	m	n	o	p	q	r	s	t	u	v
1	6.8170	1.0000	0.0056	0.0045	0.0036	0.0035	0.0026	0.0049	0.0036	0.0037	0.0025	0.0019	0.0013
2	1.5428	2.1021	0.0038	0.0185	0.0121	0.0273	0.0001	0.0020	0.0043	0.0119	0.0008	0.0006	0.0490
3	1.1504	2.4342	0.0031	0.0075	0.0239	0.0173	0.1314	0.0090	0.0147	0.0558	0.1896	0.0096	0.1564
4	1.0435	2.5559	0.0072	0.0216	0.0297	0.0000	0.0781	0.0016	0.1113	0.0298	0.0132	0.1721	0.0235
5	0.9794	2.6383	0.0138	0.0219	0.0100	0.0214	0.0639	0.0609	0.0139	0.0175	0.0490	0.1471	0.0001
6	0.9410	2.6916	0.0000	0.0002	0.0585	0.0011	0.1352	0.0283	0.0099	0.0424	0.0795	0.1451	0.0036
7	0.9370	2.6972	0.0024	0.0000	0.1887	0.0000	0.0090	0.0012	0.0518	0.0327	0.0033	0.0990	0.0308
8	0.8960	2.7582	0.0099	0.0326	0.0853	0.0051	0.0554	0.0010	0.0049	0.0077	0.1525	0.0448	0.1365
9	0.8632	2.8103	0.0003	0.0585	0.0325	0.0037	0.0000	0.0321	0.2375	0.0265	0.0282	0.0001	0.2047
10	0.8309	2.8644	0.0067	0.0010	0.0024	0.1010	0.0307	0.0207	0.0064	0.1438	0.0000	0.2232	0.0865
11	0.7642	2.9866	0.0003	0.0063	0.0310	0.5050	0.0612	0.0085	0.0096	0.0577	0.0332	0.0505	0.0037
12	0.7365	3.0423	0.0368	0.3130	0.0007	0.0477	0.0009	0.0249	0.0000	0.1312	0.0278	0.0072	0.0000
13	0.6870	3.1500	0.0016	0.0103	0.0733	0.0208	0.0973	0.0734	0.1032	0.0405	0.0076	0.0034	0.0702
14	0.6686	3.1931	0.0125	0.0074	0.0267	0.0360	0.0703	0.0719	0.0024	0.0638	0.0085	0.0067	0.1386
15	0.6582	3.2183	0.0103	0.0559	0.0000	0.0285	0.0062	0.0774	0.1529	0.0002	0.1434	0.0259	0.0376
16	0.5952	3.3844	0.0331	0.0636	0.2826	0.0000	0.1277	0.0026	0.0129	0.0004	0.0217	0.0092	0.0174
17	0.5741	3.4460	0.0444	0.2225	0.0003	0.0006	0.0280	0.3341	0.1046	0.0517	0.1714	0.0015	0.0000
18	0.5314	3.5816	0.0002	0.0169	0.0166	0.0091	0.0360	0.0753	0.0781	0.1111	0.0132	0.0202	0.0060
19	0.4832	3.7560	0.0688	0.0864	0.0734	0.0214	0.0246	0.0213	0.0064	0.0542	0.0002	0.0125	0.0091
20	0.4651	3.8283	0.2739	0.0058	0.0426	0.0036	0.0020	0.0270	0.0019	0.0000	0.0009	0.0031	0.0219
21	0.3581	4.3634	0.4612	0.0224	0.0053	0.0035	0.0087	0.0428	0.0319	0.0581	0.0000	0.0106	0.0002
22	0.3153	4.6499	0.0040	0.0028	0.0010	0.0044	0.0199	0.0001	0.0043	0.0384	0.0508	0.0013	0.0012
23	0.1620	6.4878	0.0004	0.0206	0.0000	0.1391	0.0108	0.0790	0.0334	0.0208	0.0028	0.0043	0.0019

+=Intercept, a=Age >60, b=Male, c=Arrival by ambulance, d=Monitored in the emergency department, e=Active smoker, f=Family history of coronary artery disease, g=Metabolic disease (hypertension and diabetes), h=Congestive heart failure, i=Renal failure, j=Atrial fibrillation/flutter, k=Pulmonary embolism, l=Cholesterol-lowering medications, m=Crushing/pressure, n=Exertional chest pain, o=Pain radiating to the arm or jaw, p=Symptoms relived by nitroglycerin, q=Associated shortness of breath, r=Heart rate <60 or >100 beats per minute, s=Systolic blood pressure <90 or >160 mmHg, t=Respiratory rate <12 or >20 breaths per minute , u=Final electrocardiogram interpretation suggestive of infarction or ischemia not known to be old, v= QTc>500ms

Appendix 10. Mean, median and mode of collected vital signs that were transformed into categorical variables.

	Mean	Median (± standard deviation)	Mode
Heart rate (beats per minute)	81.7	80 (±17.6)	80
Respiratory rate (breaths per minute)	17.5	16 (± 2.5)	16
Systolic blood pressure (mmHg)	140.6	138 (± 23.1)	138
Diastolic blood pressure (mmHg)	81.9	82 (± 12.3)	83
Temperature (°C)	36.5	36.6 (± 0.5)	36.7
Oxygen saturation (%)	97.1	98 (± 5.99)	98