Accelerated Diagnostic Protocols for Evaluating Patients with Chest Pain to Improve Emergency Department Efficiency

by

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Abstract

Most emergency departments (ED) within North America report issues with overcrowding. Overcrowding is defined as an inability to provide quality care in an appropriate time course to ED patients. Delays to see a care provider produce poor patient outcomes; recent research demonstrates corresponding increased time to antibiotics for infection, treatment for asthma and COPD, and increased overall mortality. Interventions to mitigate ED crowding appear justified, when supported by research.

Chest pain is the second most common ED presenting complaint in Canada. The approach to chest pain is an ideal condition to address when considering potential ways to mitigate overcrowding. Cardiac biomarkers, accelerated diagnostic protocols (ADP), and scoring systems have gained attention as strategies to reliably exclude acute coronary syndrome. Plasma cardiac troponins require time to accumulate to a detectable level after cardiac muscle necrosis. Development of higher sensitivity troponin assays lead to improved sensitivity for measurement of lower troponin concentrations. We conducted a systematic review to quantitatively summarize the operational and clinical outcomes of ADPs implemented for patients with suspected cardiac chest pain. The primary outcome was ED length of stay (ED LOS). Twenty-one articles involving 248,721 patients met the inclusion criteria, including three RCTs and 18 observational studies. A significant reduction in the total ED LOS was reported in 12 (67%) observational studies and two (67%) RCTs. Overall, ADP implementation helps decrease ED LOS and should be considered by hospitals or health care entities searching for strategies to improve operational efficiency; this decreased LOS is seen even in the absence of any change in troponin assay type. The decrease in LOS did not come at the cost of increased hospital admissions or more patients

experiencing subsequent adverse events (e.g., major adverse cardiovascular events [MACE], heart failure, strokes, etc.). The observed benefits translated across multiple health regions.

We conducted two retrospective cohort studies of all adults (≥ 18 yr) presenting to a tertiary-care, urban, Canadian ED who were triaged with a primary presenting complaint of chest pain of cardiac origin over several distinct periods of time. Firstly, we evaluated the impact of introducing an ADP and associated decrease in serial conventional troponin measurement intervals (6- to 3-hours). Compared to the identical time period in the pre-ADP period, the median ED LOS decreased by 30 minutes (95% CI: 11.2, 48.8) in the post-ADP period. Among patients who were discharged, there was a decrease in LOS by 33 minutes (95% CI: 5.3, 36.7) in the post-ADP group. Subsequently, we evaluated the impact of introducing a high-sensitivity troponin and its associated evaluation pathway at the same hospital. Compared to the identical pre-period, the median ED LOS decreased by 20 minutes (95% CI: 5.3, 36.7).) in the post-ADP period. Among patients who were discharged, there was a significant decrease in LOS by 34 minutes (95% CI: 18.1, 49.9) following the implementation of the high-sensitivity assay. Across both comparisons, the proportions of consultations, admissions, and patients experiencing major adverse cardiac events were unchanged.

Emergency department overcrowding (EDOC) will continue to feature prominently amongst the most important issues facing our healthcare system here in Canada and in many developed countries. Presentations to the ED for chest pain are, and will continue to be, a major component of ED volume. Any efforts to minimize patients' length of stay within the ED are worth evaluating as one prong of a system-wide approach to reduce EDOC.

Preface

This thesis is an original work by Jesse Hill. The research project, of which this thesis is a part received research ethics approval from the University of Alberta Health Research Ethics Board (Reference ID: Pro00096932).

Dedication

To my beautiful wife, Adrienne, whose excellence motivates me to do better.

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Chapter 1: Background

Emergency department overcrowding and the role of chest pain

Emergency Departments (Eds) are a cornerstone of the public health care system; where the laudable principles of the Canada Health Act including universality, accessibility, portability, and comprehensiveness are most tangible[1]. Unfortunately, these vital institutions are facing one of the greatest challenges in modern healthcare systems: ED overcrowding (EDOC)[2]. Overcrowding is defined as an inability to provide quality care in an appropriate time course to ED patients[3]. By no means is overcrowding a novel issue, it has been described in the health literature for at least four decades[4]. Similarly, EDOC is not unique to Canada or our healthcare system. There is readily available evidence of comparable issues from across the globe, including: The United States of America (USA), China, and the United Kingdom (UK)[5-8].

How common is it?

The majority of EDs within North America report issues with overcrowding. Across all 50 states within the USA, 91% of ED directors reported that overcrowding was a problem, with 39% identifying this as a daily problem[9]. The prevalence of overcrowding seemed to be magnified in high-volume and urban settings, at 96% for sites serving a population over 250,000, compared to 87% for smaller rural sites[9]. Similar survey data from Canadian hospitals shows 62% of sites experience ED overcrowding as a severe problem, 35% of whom struggle with this issue daily[10]. Again, the urban or high-volume sites were more vulnerable to EDOC. In Edmonton, Alberta, research has demonstrated that surrogate measures for EDOC, including the time admitted patients spend within the ED prior to transfer to the floor, as well as the proportion of patients who leave without being seen by a physician (LWBS), have been increasing[11]. Despite limited availability of pediatric data, single-site studies have revealed similar trends to

their adult counterparts. In one Canadian pediatric ED, the proportion of LWBS patients within the urgent triage category (Canadian Triage and Acuity Scale (CTAS) – 3) increased from 0.4% in 2002 to 2.3% in 2011[12]. A three-week study within the Cincinnati Children's Hospital revealed overcrowding 44% of the time[13]. Clearly EDOC is a common issue that spans geographic and demographic characteristics.

Causes: EDOC is complex and best understood through an input-throughput-output (ITO) model[14] within a system of care (Figure 1.1). Input measures reflect patient decisions to seek care, referrals, and ambulance presentations. Throughput refers to the time spent and processes occurring within the ED, intuitively making it the most readily actionable portion of the model for ED staff. Processes such as triage, awaiting physician assessment, laboratory and imaging time, consultation times and disposition decisions are included within throughput. Output measures include acute care bed availability, access to out-patient imaging and services, in-patient decision-making, discharge planning, and long-term-care capacity. One must also consider system-wide factors such as healthcare worker compensation strategies, pay-for-performance models, hospital performance targets, and public reporting.

Timely access to inpatient space is undoubtedly a driving factor for EDOC[2,3,15]. In Canada, most hospitals operate at occupancy percentages over 95%[3]. According to the Organization for Economic Co-Operation and Development (OECD), between the years 1990-2017 the number of hospital beds per 1000 patients in Canada has decreased by 63% (6.8 to 2.5)[16]. This places Canada 33rd out of 36 OECD countries in this regard, despite having the 7th highest healthcare expenditure (10.7% GDP)[16]. Given this finding, clinicians in the ED and their colleagues have developed out-patient management strategies for common previously admitted conditions (e.g., venous thromboembolism, cellulitis, asthma, pneumonia, etc.). Some conditions

still necessitate admission (e.g., myocardial infarctions, strokes, sepsis, etc.) and in many parts of Canada admissions to these limited inpatient spaces requires involving a specialist consultant in patient care and this has been shown to independently increase ED LOS[17].

Consequences: EDOC has real consequences, both obvious, and unintended. Increased patient wait times are perhaps the most readily apparent and often reported on by media. Delays to see a care provider produces poor patient outcomes; recent research demonstrates that EDOC leads to increased time to antibiotics[18], and increased mortality[19]. Furthermore, previous research has demonstrated that the proportion of patients who leave the department without being seen by a physician (LWBS), or leave after being assessed, against medical advice (LAMA) increases with worsening ED wait times[20-22]. Both LWBS and LAMA patients are at higher risk of morbidity and mortality[20]. Crowding causes increased healthcare system costs, as admitted patients have longer average inpatient lengths of stay[23]. Another by-product of EDOC include patient and provider dissatisfaction with the healthcare system. Patients with a hospital course complicated by EDOC report decreased satisfaction with their experience[24]. This seems self-evident; however, importantly, the poor experiences cause patients to decrease their likelihood of recommending the ED and the hospital at large to friends[25]. In an era where mistrust of healthcare is on the rise, patients' perception of care must be an important consideration. Healthcare professionals also suffer while working in a setting of EDOC, with both physicians[26] and nurses[27] reporting increased job dissatisfaction, depression/anxiety, absenteeism and presenteeism in this environment. Furthermore, EDOC is identified as a cause of compassion fatigue and burnout among ED physicians and nurses which can lead to poor quality care and increased medical errors[28].

Interventions: Given the decades-long struggle of healthcare systems with EDOC, it is perhaps not surprising to learn that many solutions have been proposed, implemented, and evaluated. These interventions can be categorized using the same ITO model previously described.

In-put interventions: There are three means by which patients arrive to the ED: via referral, ambulance, or self-presentation. A common belief is that low-acuity patients constitute a significant portion of the EDOC burden and that this input could be diverted to primary care[29]. This belief seems intuitive and was supported by early research into EDOC which demonstrated almost half of patients in an ED waiting room cited barriers to accessing primary care as their main reason for accessing the ED, while only 13% had clinical conditions which would require tertiary ED care[5]. Subsequent research has repeatedly demonstrated this belief to be false[15,30]. Essentially, the types of patients who contribute to overcrowding tend to be of a higher acuity (CTAS 1,2,3) and would often be referred on to an ED even if they originally presented to primary care[31]. To illustrate: an average of 16 low-complexity patients arrive to ED per eight hours in a 2007 Ottawa-based study, leading to only an 8.6 minute increase in mean ED length of stay (LOS) for all other higher-complexity patients[15].

Ambulance diversion (AD) is both a surrogate metric for EDOC, as well as a strategy to mitigate its effect. Within an urban setting, where EDOC is most pronounced, there are often multiple tertiary care hospitals. Diversion can be enacted when a specific site becomes overwhelmed with patients and ambulance crews in the region will transport patients to other hospitals. Setting thresholds for when to initiate diversion is not an exact science, there is recent simulation data to suggest that the optimal timing is as soon as the number of patients in the ED (including the waiting room) reaches the number of total care spaces[32]. AD is controversial and

is not consequence free; patients with time-sensitive conditions, such as myocardial infarction, experience higher mortality when treated in regions with high AD[33]. More research is accumulating to suggest that AD is only minimally effective to reduce EDOC; indeed, in 2009 Massachusetts instituted a statewide ban on AD and did not see any corresponding increase in ED length of stay at nine major Boston hospitals[34]. Other attempts to modify input measures have proven to be largely ineffective, and perhaps harmful, as a means to combat EDOC.

Through-put interventions: Throughput refers to the time and processes occurring while patients are physically present in the ED. A significant portion of patient LOS is spent after triage but prior to initial physician assessment, most notably in patients who are not eventually admitted to hospital[35]. Triage nurse ordering (TNO) is one proposed method to utilize the post-triage, pre-assessment period. Specific presenting complaints are given protocolized order sets and allow the triage nurse to facilitate diagnostic testing in advance of initial physician assessment. Typically, these order sets are derived from a combination of local practice, consensus documents and clinical practice guidelines[36]. Retrospective data from 2011 did show a 16% reduction in mean ED treatment time, defined as the time from placement in a treatment room until disposition, after initiation of a TNO for chest pain[37]. In a similar vein, triage liaison physicians (TLPs) who facilitate early investigation and treatment prior to patients reaching the formal care areas decrease LOS and the number of patients who left prior to being seen[38].

Altering the physical environment of the ED is another proposed intervention. Merely increasing the physical space in the ED is ineffective, with no change in ED LOS and prolonged time spent in ED after admission to hospital[39]. Conversely, ED "fast-tracks", dedicated areas within the department for low-complexity patients, have consistently led to modest reductions in patient LOS[40-42]. Patients seen in an intake or rapid assessment unit (RAU), may also benefit

from cohorting. Short-stay units or observational units are designated patient care spaces, within or near-to the ED where patients may be transferred to receive standard treatment, undergo observation, or await specific testing. Patients may spend up to 24 hours within an observation unit prior to eventual admission or discharge and this may free up ED beds in the interim. A systematic review published in 2015 found significant reductions in total hospital LOS in three of four included studies[43]. By altering either the structure or process of ED patient flow, throughput changes have shown modest success at reducing EDOC.

Out-put interventions: After a patient completes their ED work-up they will either be discharged to their usual residence, admitted to hospital, or in some cases, be placed into a transitional care environments (e.g., rehabilitation, subacute care, or long term care). Inpatient access block is a significant consequence of the very high hospital occupancy rates in Canada. Patients may remain in the ED for many hours after they have been admitted, and any longer than eight hours is considered access block[44]. Employing care-coordinators to help expedite disposition for patients arriving from or needing long-term care has been shown to reduce ED LOS[44]. Bed managers with directives to improve the efficiency of inpatient bed turnover can decrease access block; a single-site study from Kansas City demonstrated a decrease in time spent in ED post-admission from 216 minutes to 103 minutes after a full-time bed manager was hired[45]. Medical admission units (MAUs) have been proposed to expedite care in the first 72 hours of admission to limit the number of patients arriving on an inpatient floor; however, the evidence is weak for these.

Beyond operational efficiency, there has been a push for more outpatient treatments to help relieve the burden from hospitals. To illustrate: deep-vein thrombosis, a blood clotting condition that previously required hospital admission is now increasingly managed with

outpatient blood thinners and close follow-up[46]. Rapid access to out-patient clinics (e.g., orthopedics, stroke, infectious diseases, etc.), reduce the strain on in-patient capacity. Acute care capacity is not readily modifiable and as such, creative solutions are needed to improve output.

System-wide interventions: The issue of EDOC is symptomatic of a larger issue within a healthcare system, and system-wide changes have been proposed to mitigate EDOC. The UK 4-hour rule[47] is an early example of systems-based initiatives whereby hospital funding incentives were tied to meeting a target of 98% of patients having an ED LOS less than four hours. The proportion of patients meeting this target improved from 84% in 2003 to 96% in 2006[47]. Within Canada, an incentive-based program designed to reward hospitals who met ED LOS targets with additional funding produced mixed results, with some sites seeing dramatic improvements while others remained stagnant[48]. System-wide changes have shown success and should continue to be explored to reduce delays, increase evidence-based care, and improve outcomes.

Chest Pain and EDOC

Chest pain is the second most common emergency department (ED) presenting complaint in Canada[49]. It is associated with a severe practice variation, high cost of investigation[50,51], frequent consultation, and a high proportion of admissions to hospital[52,53]. Patients with chest pain may have cardiac (e.g., pericarditis, angina, myocardial infarction, etc.), respiratory (e.g., pneumothorax, pneumonia, pulmonary embolism, pleurisy, etc.), muscular, referred pain and other causes to explain their conditions. Given the frequency of presentations, the length of stay and potential for missed acute myocardial infarction (AMI) and high-risk patients, the approach to non-ST-segment elevation myocardial infarction (NSTEMI) chest pain is an ideal condition to address when considering potential through-put interventions to address EDOC.

Approach: Following a history and physical examination, most ED physicians investigate patients presenting with chest pain by ordering an electrocardiogram (ECG), chest radiograph, complete blood count and electrolytes, cardiac biomarkers (e.g., troponin), plus or minus special investigations (e.g., D-dimer, advanced imaging, etc.)

History: To establish the chest pain etiology, many physicians will have patients characterize the pain in detail, as well as elucidate risk factors for specific conditions. Important pain characteristics include pain location, onset, duration, any radiation, exacerbating and relieving factors, as well as response to treatment. Well-established risk factors for coronary artery disease are hypertension, diabetes mellitus, smoking, family history of early heart disease, as well as personal history of coronary artery disease[54]. Likelihood of a pulmonary embolism may also be explored by asking about history of blood clots, calf pain, malignancy, hemoptysis, travel, immobilization, and oral contraceptive use[55].

Physical: Vitals signs, including heart rate, blood pressure, and oxygen saturation, are universally obtained and may help steer clinicians down specific diagnostic algorithms. Cardiac and lung field auscultation, as well as pulse characteristics are also key. Obvious signs of heart failure may also be detected, including peripheral edema. In most cases, patients with chest pain in the ED, have a normal or non-contributory physical exam.

ECG: A timely ECG is essential for all ED patients presenting with chest pain. ECG interpretation is complex and may provide insight into a variety of cardiac conduction abnormalities, both benign and pathologic. Clearly, if the ECG shows an ST-segment elevation myocardial infarction (STEMI), dynamic ST segment changes or T wave changes , cardiology consultation and in-patient management are indicated. In most cases, patients with chest pain in the ED have a normal or non-diagnostic ECG.

Simple chest imaging: Clinicians obtain chest radiography to detect an enlarged cardiac silhouette, suggestive of congestive heart failure, a widened mediastinum, suggestive of aortic dissection, consolidation consistent with infection, lung infarction consistent with pulmonary embolism, as well as other primary respiratory causes of chest pain. For most presentations of chest pain, the x-ray imaging will be non-contributory.

Electrolytes: Certain electrolyte abnormalities may precipitate arrhythmias and chest pain. Hyperkalemia (elevated serum potassium) is a common cause of arrhythmias seen in the ED, especially in the context of renal failure. Abnormal levels of both calcium and magnesium can also lead to arrythmias which could cause chest pain. For most presentations of chest pain, the results of electrolyte testing will be of limited utility.

Complete blood count: Significant anemia can lead to a demand-based cardiac ischemia, especially in the context of physical exertion, and can be quickly assessed by checking each patient's hemoglobin. For most presentations of chest pain, the results of CBC testing will be normal.

Cardiac biomarkers: Cardiac biomarkers have been the focus of attention as a means of establishing safety with acute coronary syndrome (ACS) and a low probability of subsequent 30-day major adverse cardiac events (MACE)[56]. Cardiac troponin (Tn) is a protein which helps regulate the contractility of muscle, is released when myocardial cells are damaged, and represents an ideal biomarker for cardiac injury as it seems to only be expressed in myocardial tissue. Troponins takes time to accumulate to a detectable level after cardiac muscle necrosis. To accommodate for this rise, guidelines[57] have recommended measuring a repeat troponin level several hours after the initial test. Assessment of chest pain with a conventional troponin (cTn) historically required at least a 6-hour serial measurement to have adequate sensitivity as a rule-

out tool for ACS. Given that the remainder of the ED workup for chest pain may take approximately 1-2 hours, the 6-hour serial troponin is a cause of prolonged ED stays. Bedside troponin measurement was proposed as an intervention designed to reduce delays in the ED reporting of Tn; however, quality assurance concerns and improvements in central lab reporting have limited the utility of this strategy. Over the past two decades there have been advances in cardiac biomarker assays. Conventional troponin detection thresholds improved from 0.10 ug/L to 0.04 ug/L with the introduction of the Ultra TnI in 2007[58]. This lower detection threshold was combined with clinical decision rules to evaluate the safety of accelerated diagnostic protocols, with lower serial measurement intervals.

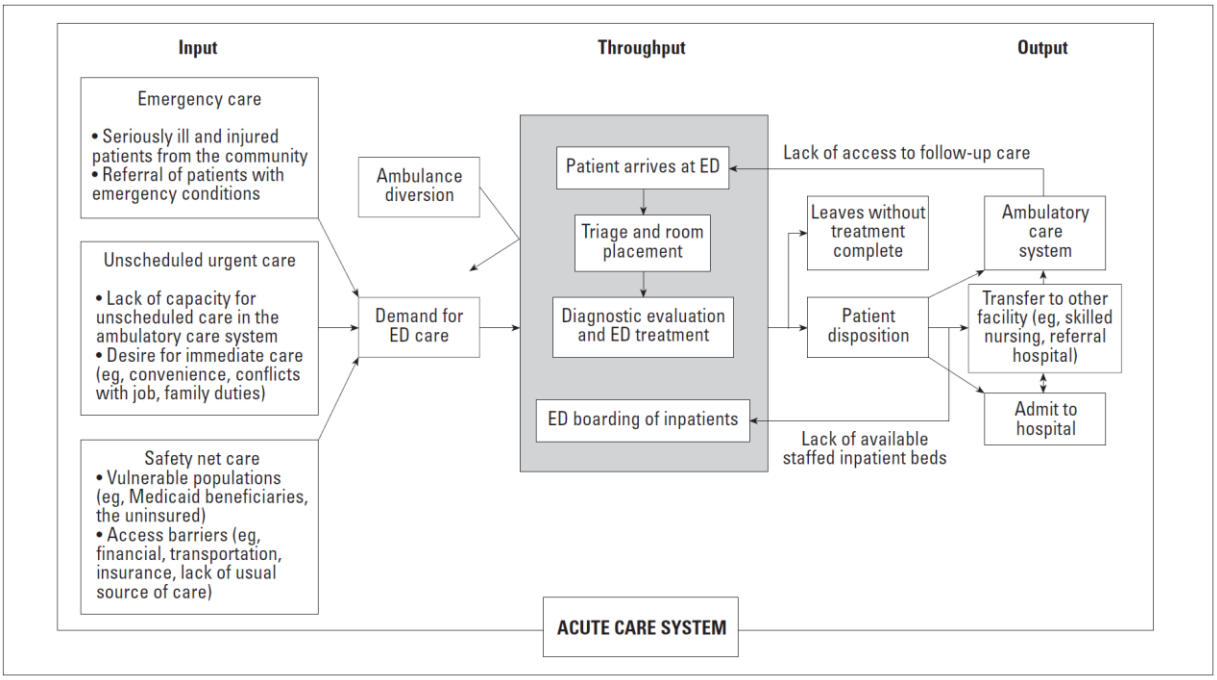
Pathways: When the initial investigations are normal, deciding which patients can be safely discharged is a fundamental consideration for clinicians practicing in emergency medicine. Unfortunately, chest pain is associated with a high rate of seven-day ED relapse requiring hospital admission[59] and poor outcomes. Due to both its prevalence and potential severity, there has been significant research focused on standardizing assessment and risk stratification for chest pain. The HEART pathway (Figure 1.2) has particular importance for ED use, as it was validated with an ED population[60]; this pathway combines a risk stratification tool, the HEART score, with serial troponin measurements. The HEART score is calculated based on history, ECG findings, age, risk factors, and troponin measurements. The original HEART study used a troponin detection threshold of 0.04 ug/L and was able to establish the safety of a 3-hour serial measurement to detect MACE with an acceptable negative predictive value. Consequently, the 2015 AHA guidelines endorsed the use of this accelerated protocol[61].

Given the intuitive possibility of increased ED efficiency with the use of an accelerated diagnostic protocol, there has been a relative paucity of operational outcomes research.

Decreased ED LOS has been demonstrated in two studies; however, one study excluded all discharged patients[62], and the other only had 11% of patients discharged home from ED[63]. This low rate of discharge is due, in part, to the availability of observational units, which are not commonly in use within the Canadian healthcare system. Observational data from Calgary, Alberta, demonstrated a 30-minute reduction in total ED LOS after the transition from a 6-hour conventional Tn assay to a 2-hour serial high sensitivity (hs) - troponin T (hs-TnT), with no change in either cardiology consultation or admission rates[64]. An academic hospital in Edmonton, the Royal Alexandra Hospital (RAH), has operated with different chest pain protocols based on troponin laboratory reporting. These changes represent an ideal opportunity to study the impact of decreasing the duration of serial troponin measurements on EDOC. This MSc thesis will aim to evaluate the implications on emergency department efficiency of the implementation of accelerated diagnostic protocols for chest pain. Specifically, we will describe the ED LOS, consultations, outcomes, and follow-up of patients with cardiac (CTAS 2) and non-cardiac (CTAS 3) chest pain presenting to a tertiary care ED with different CP protocols.

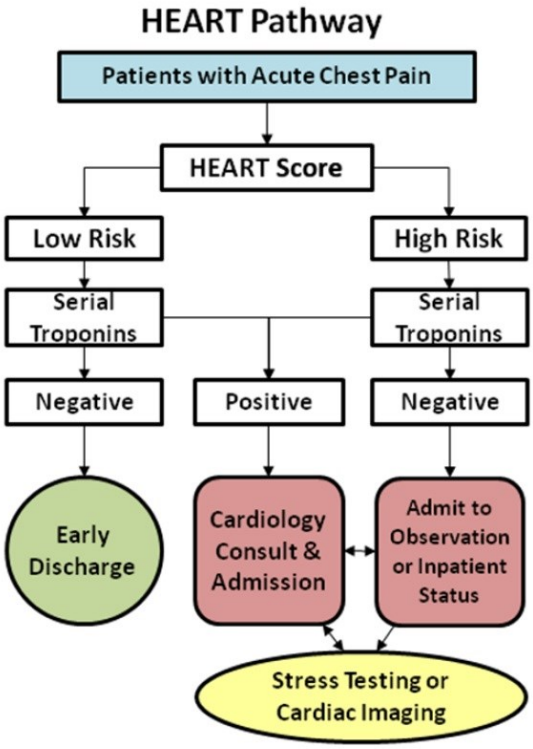
Figures

Figure 1.1 Input-throughput-output conceptual model for emergency department overcrowding.



Adapted from "A Conceptual Model of Emergency Department Crowding," by BR Asplin et al, 2003, *Annals of Emergency* Medicine, 42:176.

Figure 1.2 The HEART Pathway.



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Chapter 2: Summary of Available Evidence

Introduction

Emergency departments (EDs) are facing one of the greatest challenges in modern healthcare systems: ED overcrowding (EDOC)[1]. Overcrowding is defined as an inability to provide timely and evidence-based care to ED patients[2]. Overcrowding in the ED has real consequences, both obvious, and unintended. Increased patient wait times are perhaps the most readily apparent consequence of EDOC and are often reported by the media. Delays in seeing a care provider, however, also produce poor patient outcomes[3], including increased mortality[4].

Chest pain is a high-volume ED presentation, the second most common in Canada[5], and has been a focus of interventions aimed at improving efficiency. Scoring systems for the assessment of chest pain have been developed to provide pre-test probabilities of serious conditions[6]. In addition, protocols for ED assessment of patients with chest pain have also been implemented. Finally, rapid advances in myocardial biomarkers, such as troponin (Tn), and access in the ED have increased the confidence to ED physicians regarding the use of these protocols.

Tn accumulates in blood after cardiac muscle necrosis and rising levels act as a surrogate marker of acute coronary syndromes (ACS). Early conventional Tn assays historically required at least 6-hour serial measurements to achieve adequate sensitivity as a rule-out tool for ACS. Given that the remainder of the ED workup for chest pain may take approximately 1-2 hours, the 6-hour serial Tn contributes to a longer ED LOS. Over the past two decades there have been advances in cardiac biomarker assays. Tn detection thresholds improved from 0.10 μg/L to 0.04 μg/L with the introduction of a high-sensitivity troponin (hsTn) in 2007[7]. This lower detection threshold was added to clinical decision rules to create accelerated diagnostic protocols (ADPs),

with lower serial Tn measurement intervals. Ongoing improvements to hsTn measurements have led to detection thresholds as low as 2-3 ng/L, allowing for rising levels to be detected with as little as a 1-hour serial measurement[8].

Given the intuitive possibility of increased ED efficiency with the use of an ADP, there has been an increase in studies pertaining to operational outcomes. Many studies have focused on the safety of ADPs, specifically their ability to determine which patients are at high risk of developing a major adverse cardiac event (MACE) within 30 days. Once the safety profile was determined to be acceptable, the focus in recent years has shifted to efficiency. The purpose of this study was to quantitatively summarize the operational and clinical outcomes, specifically ED LOS as well as MACE and admission proportions, of ADPs implemented for patients with suspected cardiac chest pain.

Methods

Protocol: A protocol was developed a priori to define the objectives, search strategy, eligibility criteria, outcomes, procedure for extracting and analyzing information from included studies, and data analysis. This systematic review conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was registered in PROSPERO (registration number: CRD42021249679).

Search strategy: A comprehensive search of electronic databases (MEDLINE (OVID), Embase (OVID), Cochrane Trials (Wiley), CINAHL(EBSCO), LILACS, SCOPUS, and Dissertations and Theses Global (Proquest)) was completed from database inception to April 9, 2021. The search strategy was conducted by a health science librarian (LD) based on subject headings and keywords and optimized for each database; the full search strategy is available in

the appendix. There were no exclusions of articles based on date of publication or language. Grey literature searches were conducted using Google Scholar as well as a search of clinical trial registries. Bibliographies of retrieved articles and known reviews were also searched for relevant studies.

Study selection: To be considered eligible for inclusion, studies must have implemented some form of ADP within the ED for evaluating adult (age ≥18 years) patients presenting with chest pain. Common risk stratification tools used as part of ADPs included but were not limited to the History, ECG, Age, Risk Factors, and Troponin (HEART) pathway; Emergency Department Assessment of Chest Pain Score (EDACS); and Accelerated Diagnostic protocol to Assess chest Pain using Troponin (ADAPT). The primary outcome was ED LOS defined as the time from triage to discharge (for discharged patients) or to bed request (for admitted patients). Secondary outcomes included the proportion of patients requiring admission and the proportion of patients with MACE, defined as a composite of total deaths, myocardial infarction (MI), stroke, and revascularization within 30 days of the ED presentation. Studies were required to be either randomized controlled trials (RCTs), controlled clinical trials (CCTs), before-after studies, or observational studies (prospective and retrospective) with a well-matched comparison group.

Two independent reviewers (EY and JH) identified relevant studies in a two-step process. First, from the title, abstract, or descriptors, we independently reviewed articles to identify potentially relevant studies for a full review. Second, from the full text, using specific criteria, we independently selected studies for inclusion in this review. Standardized forms with pre-defined inclusion/exclusion criteria were used. Disagreements were resolved by consensus between the two reviewers; reasons for exclusion were documented. Agreement was measured and reported using kappa (κ) statistics with 95% confidence intervals (CI).

Risk of bias assessment: The risk of bias of RCT/CCT's was assessed using the Cochrane Risk of Bias (RoB) tool[9]. The RoB tool assesses the risk of bias in RCTs using a fixed set of domains of bias, focusing on different aspects of trial design, conduct, and reporting. Studies could be judged as having a "low" or "high" risk of bias or the reviewer could express "some concerns. The quality of observational cohort studies was assessed using the Newcastle-Ottawa assessment scale (NOS)[10]. The NOS uses a star system to appraise bias in three domains: participant selection, comparability among groups, and assessment of exposure/outcomes. Pre-specified criteria were used to assign a RoB score to the included studies. Two reviewers (EY and NE) independently evaluated the methodological quality of the studies and disagreements were discussed and resolved with a third-party mediator (JH).

Data extraction and analysis: Data from the studies were extracted independently by two reviewers (EY and NE). Disagreements and reliability were checked by a third reviewer (JH). Inter-rate reliability was measured with a Kappa statistic (κ). Summary of findings tables were constructed including information concerning each article's source, country of origin, year of publication, design, demographics, type of Tn assay used, ADP used, ED LOS, the proportion of patients admitted, and MACE proportions. Where relevant data was missing from published articles, attempts were made to contact the authors to provide the required information. In situations where the timing associated with a Tn remained unclear, a pre-intervention serial time of six hours was assumed, in keeping with American Heart Association guidelines at the time.

Studies were pooled if they represented similar populations, outcomes, and designs, and were judged to have sufficiently low clinical heterogeneity. ED LOS as a continuous indicator was often skewed and thus reported as medians with interquartile ranges (IQRs) in a majority of the studies. Therefore, a meta-analysis was conducted with differences in median LOS by pooling

differences of medians using a random-effects model via the quantile estimation (QE) method put forth by McGrath et al[11]. This method has been found to outperform transformation-based methods in meta-analyses of median outcomes, particularly when outcome measures are skewed. In the secondary analyses, median LOS values in each subgroup were pooled via the same method. The QE methodology derives the variance for medians or differences of medians for studies reporting medians, first quartiles, and third quartiles for an outcome (scenario S_2). For the four out of 21 studies that reported mean LOS values, the QE algorithm (scenario S_4) was applied to obtain differences in medians and their variances. Between-study heterogeneity was assessed in each analysis using I^2 statistics with the values of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively. Meta-regression analysis was conducted considering each study as an individual sample; the main variables for consideration were the presence of hsTn, pre-intervention LOS, and decrease in serial Tn measurement time.

All statistical computations were performed using RStudio 2022.02.1 in the R 4.2.0 environment (The R Development Core Team, Vienna, Austria) with the packages *metafor* and *metamedian*. The weights given to each study in the pooled analysis were based on the Mantel Haenszel method. Descriptive analysis of the data was performed if the heterogeneity among the studies or insufficient outcome reporting, prohibited the data pooling.

Readers will be alerted if there is substantial heterogeneity ($I^2 > 50\%$) and encouraged to interpret all aggregated results cautiously. Assuming sufficient heterogeneity and outcome reporting allowed for a meta-analysis, several sensitivity analyses were completed including fixed effects as well as study quality assessment (in which studies with a high risk of bias studies were excluded).

Subgroup/sensitivity analysis: Assuming sufficient heterogeneity and outcome reporting allowed for a meta-analysis, several subgroup/sensitivity analyses were planned. Subgroup analysis of the primary outcome (ED LOS) included specific Tn delta times.

Results

Our search strategy generated 5507 citations. After accounting for duplicates and performing a title and abstract screen, a total of 165 articles underwent full-text review. Twenty-one articles involving a total of 248,721 patients met the inclusion criteria ($\kappa = 0.62$; 95% CI: 0.47 to 0.77) (Figure 1). Of the 144 articles excluded, the most common reasons were no ED LOS data reported (n=74), no comparison to ADP (n=22), and non-ED management (n=10) (Figure 1). Among the 21 included studies, there were three RCTs[12-14] and 18 observational studies[15-32] (Table 1). Three studies[13,15,22] reported changes in ED LOS specific to discharged patients, the remaining studies reported LOS changes for all patients.

Study characteristics: As shown in Table 1, the included studies represented a diverse patient group, drawn from populations on four different continents (North America, Asia, Europe, and Australia). ED characteristics were also varied, ranging from sites with an annual census of 12,000 to 200,000 patients. The included studies were most frequently conducted in the United States of America (n=7) and Australia (n=6). Due to the recency with which ADPs have entered clinical practice, there was a preponderance of recent publications, with 48% (n=10) of included studies published after 2020.

The sample sizes for individual studies ranged from 130 to 54,468, with a median of 3288 (IQR: 1233, 12630). The average ages ranged from 51.9 (±1.2) to 71.6 (±13.2). Female patients represented 32–60% of patients in the included studies.

Methodological quality of studies: The overall risk of bias for the three included randomized trials was low (Supplementary Figure 1). One study[13] was open label although otherwise methodologically rigorous. The included observational studies were of variable quality, with median NOS scores of eight (IQR: 6, 9).

Outcomes: A significant reduction in the total ED LOS was reported in 12 observational studies[16-18,21,24-26,28-32] and two RCTs[12,14](Table 2). Five studies[15,19,22,23,27] demonstrated no significant changes in LOS after implementation of an ADP, whereas one study[20] reported a significant increase.

There was a strong correlation (Pearson's correlation coefficient = 0.69,) between the baseline ED LOS and the reduction in LOS following ADP implementation (Figure 2). Linear regression of this data set reveals a predicted ED LOS of -1.6+0.44(baseline LOS). Studies that reported an initial ED LOS of greater than 7 hours all saw a reduction of over 100 minutes following the implementation of the ADP. Among the five studies with a baseline ED LOS of 4 hours or less, two showed either no change or an increase in LOS, while the remaining three reported reductions of less than 18 minutes.

Several studies[15,16,20,23,27,29,32] did not explicitly state a serial Tn time during their pre-intervention phase. Most authors were able to provide this detail when contacted; however, three studies remained unclear[1,20,32]. For these three studies, a pre-intervention time of six hours was used as a clinically relevant and standard imputation. A pre-planned meta-analysis stratified by the change in Tn serial measurement interval was conducted. The overall statistical heterogeneity (I^2) was high, and the pooled results should be interpreted cautiously. With respect to subgroups, studies reporting a delta change of 1 hour or less, were more homogenous with a pooled median reduction of 27.6 minutes (-0.46 hours; IQR: -0.58 to -0.34; Figure 3). The remaining subgroups

were significantly heterogeneous (I^2 >99%). The median of median differences was consistent with the pooled estimate for each subgroup with 30-, 72-, and 24-minute reductions for the studies reporting 0–1-, 2–3-, and >3-hour reductions in Tn interval, respectively.

Seven studies transitioned from a conventional to hsTn[18-20,22,25,31,32]. Four of these studies demonstrated a significant change in LOS following the hsTn[18,20,25,31]. When pooled for meta-analysis, there was high heterogeneity among these studies and the results should be interpreted cautiously (I^2>96%); however, there was limited impact demonstrated on median LOS (-0.23 hours; IQR: -0.60 to 0.14; Figure 4).

A meta-regression analysis was performed to determine which clinical parameters had the largest influence on the change in ED LOS (Figure 5). Specifically, we were interested in changes in serial Tn measurement intervals, changes in hsTn assays, and pre-intervention ED LOS. Neither change in serial Tn measurement interval nor implementation of an hsTn assay were found to be significant on univariate comparisons (Figure 5). Pre-interventional ED LOS was significantly associated with change in LOS in the linear regression adjusting for the change in Tn interval time.

Observational studies implementing a 2-hour serial Tn measurement were the most likely to demonstrate a significant decrease in LOS. Six of the seven studies using this interval reported a significant decrease[17,18,21,26,29,30]. Overall, half of the studies[16,31] implementing a 3-hour interval and 40% with a 1-hour interval[25,28] reported significant reductions.

The most commonly implemented risk assessment tool was the HEART pathway (n=7)[15,17,19,20,22,23,32] (Table 2). Only one of these studies using the HEART score reported a significant decrease in LOS[17].

Admissions: Admission proportions were reported in 13 studies[15,17-24,26,28,29,32](Table 3). Given the wide variety of healthcare regions, there was a correspondingly large range of admission proportions from 8.8%[17] to 68.3%[26]. No study reported an increase in the proportion of patients admitted after the introduction of an ADP. Eight studies[15,17,19-23,26] reported a significant decrease in admissions. The largest decrease in admission proportion was a 26% reduction, with an adjusted odds ratio of 0.33 (95% CI 0.25-0.42) for admission in the post-implementation phase[22]. There was no significant difference in admission proportions following the introduction of an ADP in the Canadian context[18].

MACE: MACE within 30 days was reported in six observational studies[16,19,22,23,28,30] and all three RCTs[12-14]. One observational study[24] reported a 45-day MACE. Two large studies reported the lowest proportion of patients experiencing MACE at 0.30% and 0.35%[12,16]. On the high end, a MACE proportion of up to 19% was reported[28]. No study reported a significant difference between the proportion of patients experiencing MACE before and after the implementation of the intervention.

Discussion

This systematic review provides a comprehensive summary of the operational and patient-oriented clinical outcomes following the introduction of ADPs in ED settings. Overall, 21 studies were identified for inclusion in the present review. These studies represent a largely North American sample, despite having representation from Europe, Asia, and Australasia. Likewise, the included studies were diverse in size, ranging from small observational studies to large RCTs or studies utilizing administrative datasets. Most studies were single centered (n=11). Notably, despite the limitations of data pooling due to high heterogeneity among the studies, our

results show that using an ADP, generally accompanied by a hsTn, resulted in lower ED LOS in the majority of studies. Overall, 68% of studies demonstrated a significant reduction in ED LOS. These reported reductions range from a modest 18 minutes[30] to an impressively large 4.5 hours[25].

There was a strong correlation between pre-intervention ED LOS and post-intervention reduction in ED LOS. This relationship was reflected in both the descriptive Pearson's correlation analysis, as well as the meta-regression. This seems intuitive as it is reasonable to expect a larger ability to influence LOS when initial wait times are longer. Studies with an initial LOS of less than 7 hours did not report decreases exceeding 1 hour. One consideration for minimal reductions in these EDs may be due to wait times rather than protocol efficiency. Patient wait times (e.g., time form triage to room placement, and time from placement to physician initial assessment [PIA]) were not frequently reported in the included studies, and while there is certainly considerable variation among healthcare systems, many patients are likely waiting up to several hours prior to PIA. Given that this time prior to physician assessment is not modifiable by an ADP, sites with a low baseline ED LOS may have very little modifiable time and hence their corresponding modest reductions.

Another possible explanation is that a significant number of patients undergo only a single Tn measurement. If a patient is evaluated in a time frame beyond the serial measurement interval dictated by whichever Tn protocol is being employed, then a single initial negative result may be sufficient to rule out cardiac ischemia. In this scenario, the addition of an ADP would be expected to have little to no impact, as patients dispositioned after a single Tn assay are unaffected by the timing of serial measurement. Only two studies[21,29] restricted enrollment to patients undergoing two or more Tn measurements. Both studies saw significant reductions in ED LOS of over 1.5 hours. We recommend that future publications aim to include more robust

reporting for LOS outcomes, more granular reporting of ED times such as PIA, and stratify patients based on the number of Tn tests ordered. This will improve the granularity of the intervention and provide an assessment of which scenarios these protocols have the greatest impact on efficiency.

Several authors cited a lack of familiarity with and uptake of ADP usage[16,20,23,31] as possible factors contributing to the modest reductions in ED LOS. In other studies, this was anticipated and mitigated. The trial design for the study conducted by Anand et al[12]. was particularly robust and included a randomization period of several months where hospitals and practitioners became familiar with the usage of the ADP and an assay, prior to the true implementation phase. In addition to eliminating very lengthy serial Tn measurement intervals (up to 12 hours), this randomization period likely contributed to the large effect size observed.

The only study to report an increase in LOS implemented the HEART score in conjunction with a new hsTn assay[20]. While the authors did not state any specific Tn interval prior to their study, they suggested that the new measures encouraged more frequent serial testing as well as some provider unfamiliarity with using an ADP which drove the increase in time spent in the ED.

The management of ED presentations for chest pain varied dramatically among some of the regions with included studies. This is perhaps best illustrated by the difference between the admission proportion in Canada compared to Australia. In the Canadian study[18], only 8.8% of patients were admitted and there was a strong focus on outpatient management and follow-up; however, in the Australian studies reporting admission proportions[17,21,24,26], the proportion ranged from 40.2–68.3%. This variation was likely due to the widespread use of observational units for the further assessment of chest pain in Australia. Despite the differences in practice, it is

reassuring that no studies reported an increase in admissions following the introduction of an ADP.

One of the earlier concerns regarding the implementation of ADP was the possibility that a higher proportion of patients would experience adverse outcomes following rapid discharge due to decreased observational time in the ED. In this review, using MACE as an important 30-day outcome, no such increase in adverse events was identified. In addition, this concern has been repeatedly demonstrated by others to be false[33]. None of the studies included in the present review reported a significant change in MACE after implementing an ADP, suggesting that the implementation of chest pain protocols is safe.

Strengths and limitations

This review has both strengths and limitations that require discussion. A comprehensive search strategy was created with the help of a health sciences librarian and generated a robust number of studies for review. Efforts aimed at mitigating publication bias were employed; however, we recognize that some publications could have been missed. Our review was further strengthened by protocol registration, efforts to avoid selection bias, and a standardized data extraction process involving two independent reviewers and a third-party mediator. Additionally, the data span numerous healthcare regions which increases the external validity of our results.

Our results are limited by the fact that the included studies are predominantly observational in design. Many of the included studies included ED LOS as a secondary outcome and as such variable outcome reporting was common. There was also considerable variation in the type of ADP employed as well as the type and timing of Tn measurements. Outcome measures such as LOS were somewhat obscured by reporting results for all patients who had a Tn assay performed. Granular reporting of LOS results for the subset of patients who underwent

serial Tn measurements would allow for more definitive conclusions. There was a large degree of statistical heterogeneity across most subgroups (I^2 = 99–100%) and RCT data were combined with observational data; thus, the results of the pooled analyses should be interpreted cautiously. We believed that due to the limited potential for bias in enrollment and intervention in these non-RCT chest pain studies, it was reasonable to pool these data. While this variability speaks to the broad applicability of ADP effectiveness, it does obscure the direct comparison of individual elements.

We were concerned about skewed data, which is associated with LOS reporting, as there are often outliers with dramatically higher LOS values. From the available data, we calculated means and standard deviations using a method proposed by Wan et al.[34] to assess for differences and found no major changes from the original median and IQR data pooling. We, therefore, believed it was most appropriate to report the data as the original medians and IQRs.

Conclusions

This systematic review aimed to determine the effectiveness of ADP usage for chest pain in the ED and to explore what factors contributed to implementation success. Our findings demonstrate that implementation of an ADP helps decrease ED LOS and should be considered by hospitals or healthcare entities searching for strategies to improve operational efficiency; this decreased LOS is seen even in the absence of any change in Tn type. The decrease in LOS did not come at the cost of increased hospital admissions or more patients experiencing subsequent adverse events (such as MACE). The observed benefits also translated across multiple health regions. Further research should evaluate the optimal combination of Tn measurement interval in combination with specific ADPs.

Tables

Table 2.1 Study design and demographic characteristics of included studies.

	Author	Publication Year	Country	Sample	Age (mean±SD) or median (IQR) Before	Age (mean±SD) or median (IQR) After	Proportion female Before	Proportion female After
Before/After								
	Al Marashi	2020	Australia	634	61.3±13.6	58.7±12	48%	53%
	Allen	2018	USA	31,090	51.9±1.2	52.6±0.52	54.80%	55.90%
	Barnes	2021	Australia	2255	55±17	52±17	47%	47%
	Crowder	2015	Canada	12620	62.7	61.4	48.20%	50.10%
	Ford	2021	USA	3205	54 (39-65)	55 (41-66)	50%	49%
	Furmaga	2021	USA	12345	58.8±17.7	59.1±17.4	55.70%	58%
	Greenslade	2020	Australia	12630	61±17.2	58.1±17	41.60%	41.20%
	Ljung	2019	Sweden	1233	64 (54-74)	63 (53-71)	43%	46%
	Mahler	2018	USA	8474	54 (45-65)	54 (44-66)	52.90%	54.10%
	Mountain	2016	Australia	1029	64	64	50.30%	52.40%
	Mungai	2020	USA	300	58.6 ±10.8	57.3±8.7	49.30%	42%
	Parsonage	2017	Australia	54468	60.6±16	58.9±16.5	45.80%	46%
	Randolph	2018	USA	5064			49%	46%
	Ruangsomboon	2018	Thailand	130	71.6±13.2	66.6±14.2	43.10%	60%
	Than	2018	New Zealand	31332	65.1±16.4	65.8±16.1	46.50%	45.60%
	Than	2021	New Zealand	2416	63±13		38.20%	
	Twerenbold	2016	Switzerland	2544	64 (51-76)	59 (47-72)	32%	30%
	Vigen	2020	USA	31543	53.8±14.2	54.2±14.6	48.10%	47%
					Ctrl	**Exp**	**Ctrl**	**Exp**
RCT								
	Anand	2021	Scotland	31492	59±17	58±17	45%	46%
	Carlton	2020	UK	629	53.6±16.2	54±16.2	41%	41%
	Chew	2019	Australia	3288	58.6 (48.8-71.2)	58.7 (48.6-69.4)	46.80%	46.80%

Table 2.2 Troponin characteristics and outcomes on emergency department length of stay.

	Sample		Troponin		Troponin Interval (hr)		ADP	Median ED LOS (IQR)		
Author	**Before**	**After**	**Before**	**After**	**Before**	**After**		**Before**	**After**	**p**
Before/After										
Al Marashi	308	326	hsTnI	hsTnI	NS	3	NS	8.6	5.2	0.001
Allen	15,946	15144	TnT	TnT	6	3	HEART	6.48 (SD=0.29)	6.62 (SD = 0.51)	0.38
Barnes	1131	1124	hsTnI	hsTnI	3	2	HEART	4.3 (3.3-7.1)	3.6 (2.6-5.4)	0.001
Crowder	6866	5754	TnT	hsTnT	6	2	NS	6.6 (4.25-9.80)	6.1 (4.12-8.73)	0.001
Ford	1589	1616	TnI	hsTnT	3	1	HEART	6.2 (4.2-9.4)	6.4 (4.3-9.6)	
Furmaga	4892	7453	cTn	hsTnT	NS	1	HEART	3.47 (2.45-4.73)	3.83 (2.67-5.25)	0.01
Greenslade	5764	6866	cTn	TnI	6	2	IMPACT	9 (5.9-14.8)	7.4 (4.8-12.1)	
Ljung	612	621	cTn	hsTn	3	1	HEART	3.8 (3.1-4.9)	4.0 (2.4-4.8)	
Mahler	3713	4761	TnI	TnI	3	3	HEART	4.0 (2.8-5.2)	3.6 (2.6-5)	0.15
Mountain	426	603	TnI	TnI	12	4	NS	7.5	5.9	0.001
Mungai	150	150	TnT	hsTnT	3	1	NS	8.4 (1.9-14.8)	3.9 (0.5-8.5)	0.001
Parsonage	30769	23699	cTn	TnI	8	2	ADAPT	3.8 (2.7-5.8)	3.5 (2.4-4.9)	0.01
Randolph	4295	769	hsTn	hsTnT	6	2	NS	3.3 (3.2-3.5)	3.3 (3.0-3.7)	0.96
Ruangsomboon	65	65	hsTnT	hsTnT	3	1	NS	4.3 (3-5.4)	2.3 (1.8-3.7)	0.001
Than	11529	19803	variable	variable	6	2	Multiple	NS	Decreased 2.9 (2.4-3.4)	0.001
Than	1073	1343	hsTnI	hsTnI	2	2	COVID Path	3.8 (2.8-4.9)	3.4 (2.6-4.6)	0.0001
Twerenbold	1455	1089	cTn	hsTnT	6	3	NS	6.3 (3.8-8.7)	5.1 (3.6-7.2)	0.046
Vigen	16991	14552	TnT	hsTnT	NS	1	HEART	6.42 (4.67-9.68)	6.52 (4.87-9.27)	
RCT					**Ctrl**	**Exp**		**Ctrl**	**Exp**	
Anand	14700	16792	hsTnI	hsTnI	12	3	Other (STEACS)	10.1±4.1	6.8±4.1	0.001
Carlton	313	316	hsTn	hsTn	3	0	NS	5.0 (3.4-7.4)	4.4 (3.2-6.8)	
Chew	1642	1646	hsTnT	hsTnT	3	1	Multiple	5.6 (4-7.1)	4.6 (3.4-6.4)	0.001

Table 2.3 Proportions of admitted patients and those experiencing MACE (major adverse cardiac events) within 30 day.

			Admissions				MACE		
	Author	**Sample**	**Pre**	**Post**	**Decrease (95% CI)**	**p**	**Pre**	**Post**	**p**
Before/After									
	Allen	31,090	60.80%	52.40%	8.4% (9.7, 7.1)	0.0001	0.62%	0.35%	0.27
	Barnes	2255	41%	24%		0.001			
	Crowder	12620	8.80%	8.80%					
	Ford	3205	28%	24%	4% (7.3, 1.3)		7%	7%	
	Furmaga	12345	42.60%	31.50%	11.1% (15, 7)	0.01			
	Greenslade	12630	58.40%	49%	9.3% (11.2, 7.5)				
	Ljung	1233	59%	33%	aOR 0.33 (0.23-0.42)		1.30%	1.40%	
	Mahler	8474	61.60%	55.60%	6% (8.1, 3.9)		8.20%	8.30%	
	Mountain	1029	43.40%	40.20%		0.07	15.20%	14.30%	0.768
	Parsonage	54468	68.30%	54.90%	13.3% (18.7, 8)	0.01			
	Ruangsomboon	130	30.80%	16.90%		0.065	19%	12.80%	
	Than	2416	12.30%	9.30%					
	Than	31332					15.70%	14.90%	
	Vigen	31543	29.10%	27.20%					
RCT									
	Anand	31492					0.40%	0.30%	0.068
	Carlton	629					5%	8%	
	Chew	3288					0.97%	1.00%	0.867

Chapter 2 Figures

Figure 2.1 PRISMA flow diagram illustrating the overview of the systematic literature search.

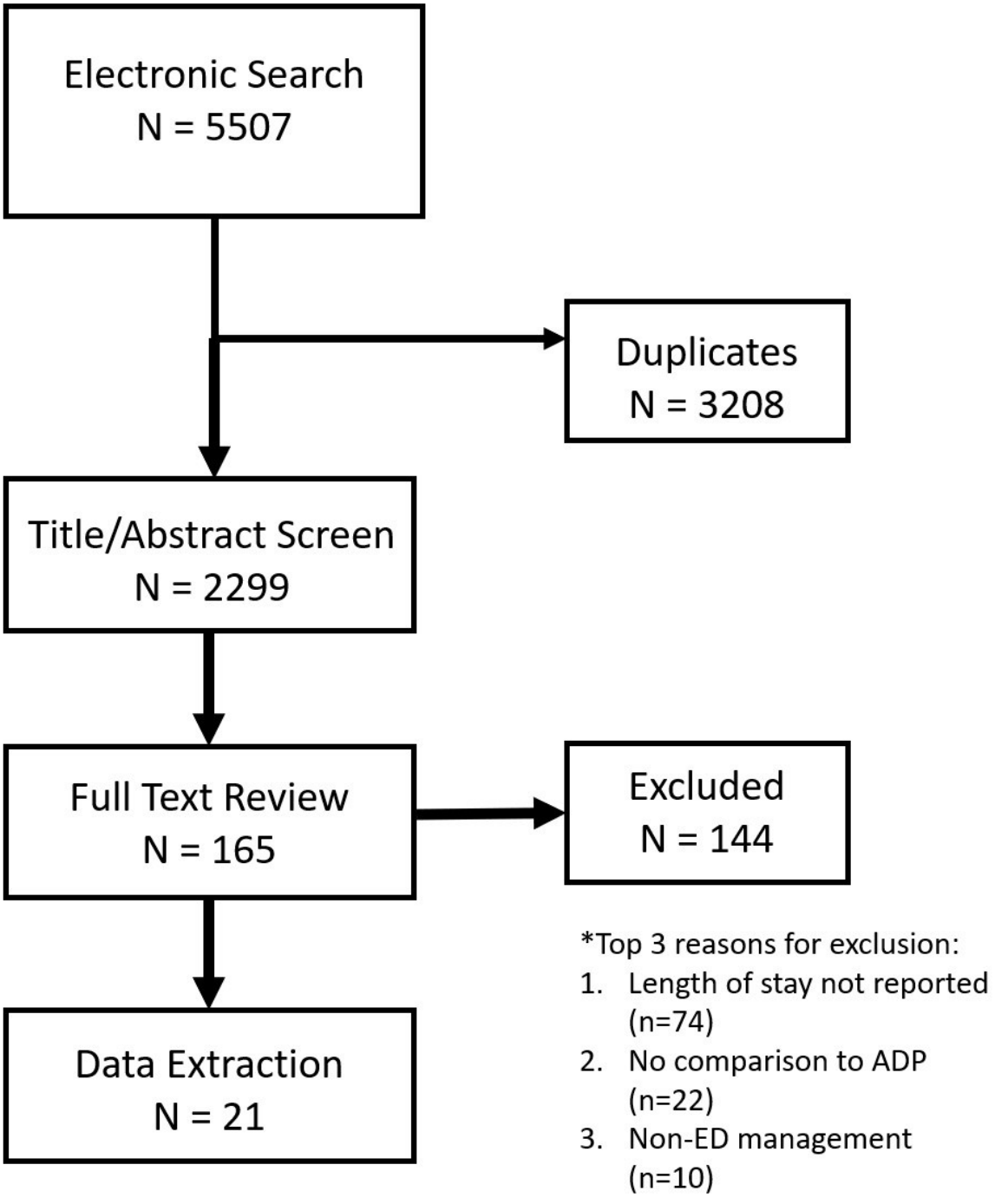


Figure 2.2 Cochrane risk of bias scores for included randomized controlled trials.

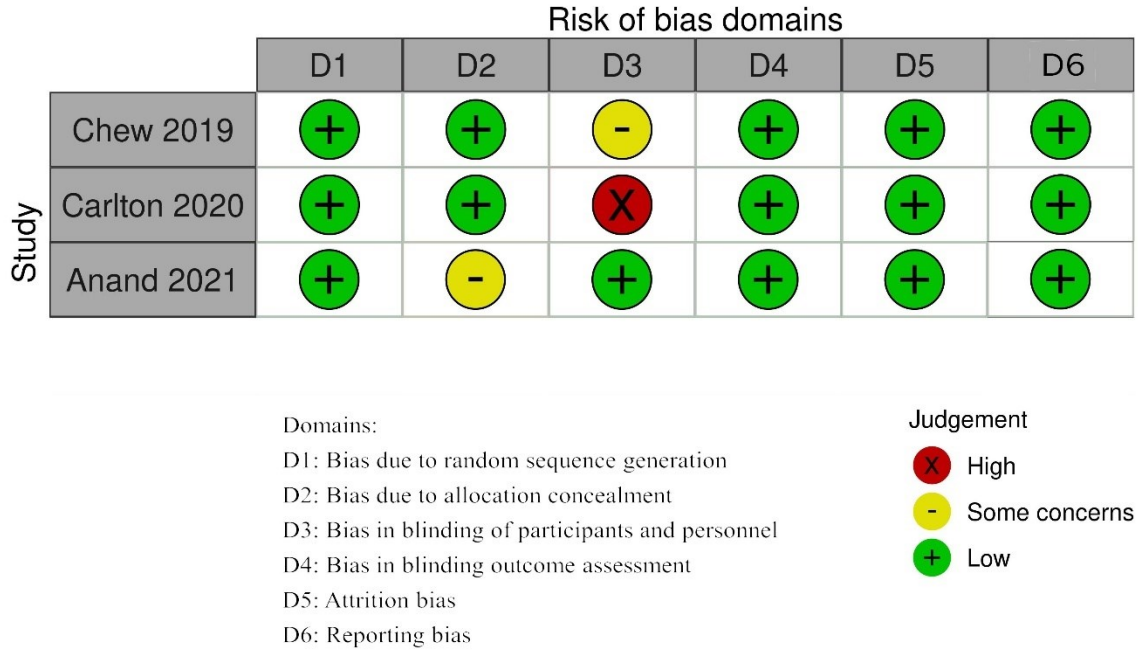


Figure 2.3 Reduction in length of stay as a function of baseline emergency department length of stay.

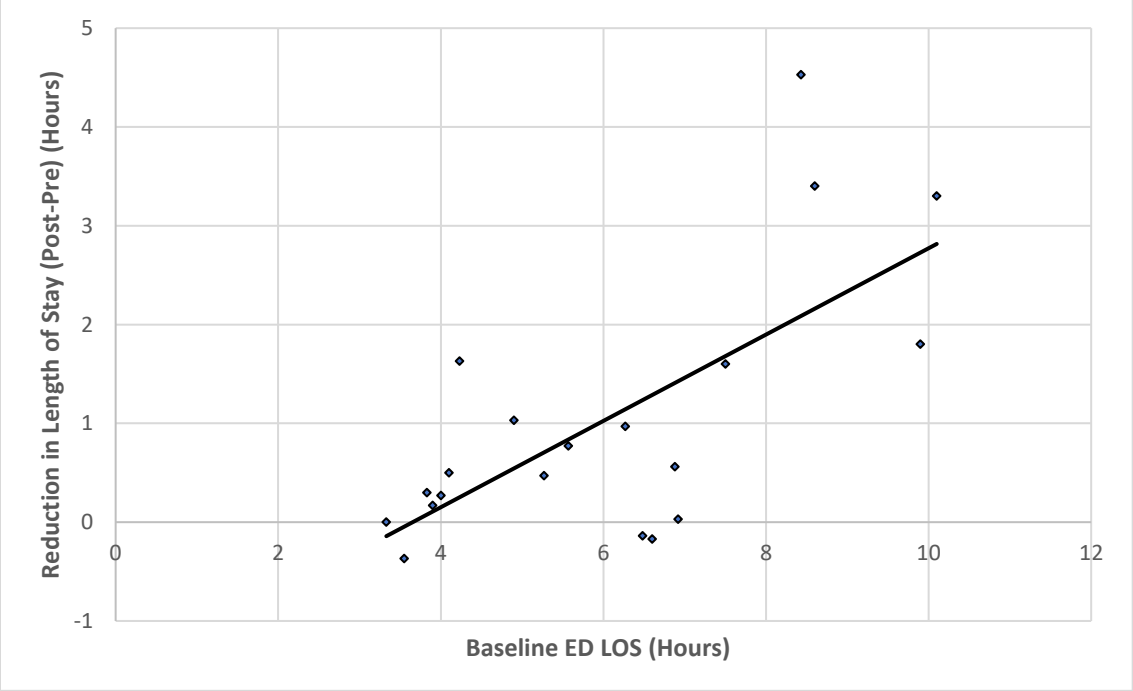
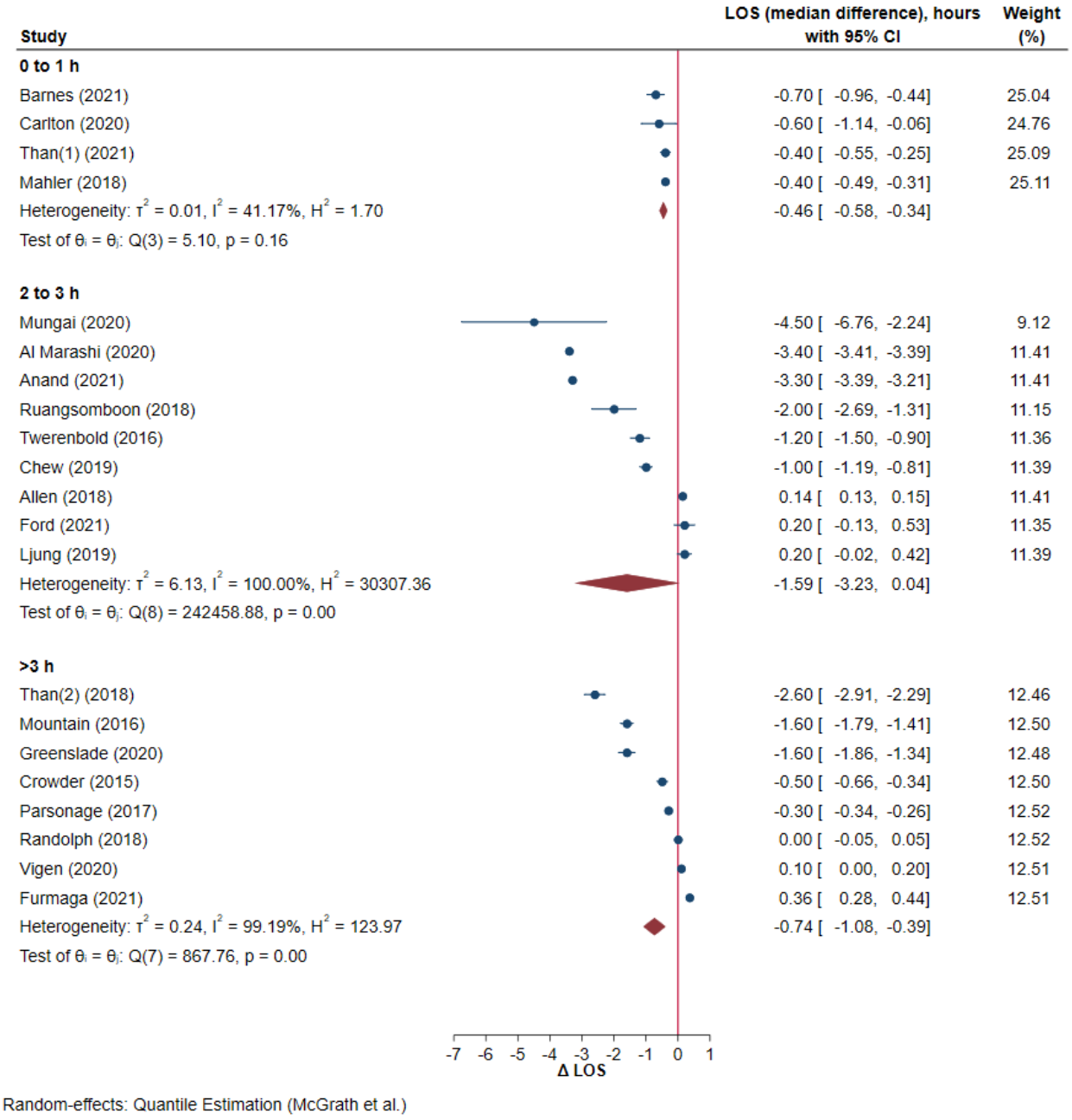


Figure 2.4 Effect of decrease in troponin interval timing on emergency department length of stay.



Random-effects: Quantile Estimation (McGrath et al.)

Figure 2.5 Effect of change from conventional to high-sensitivity troponin on emergency department length of stay.

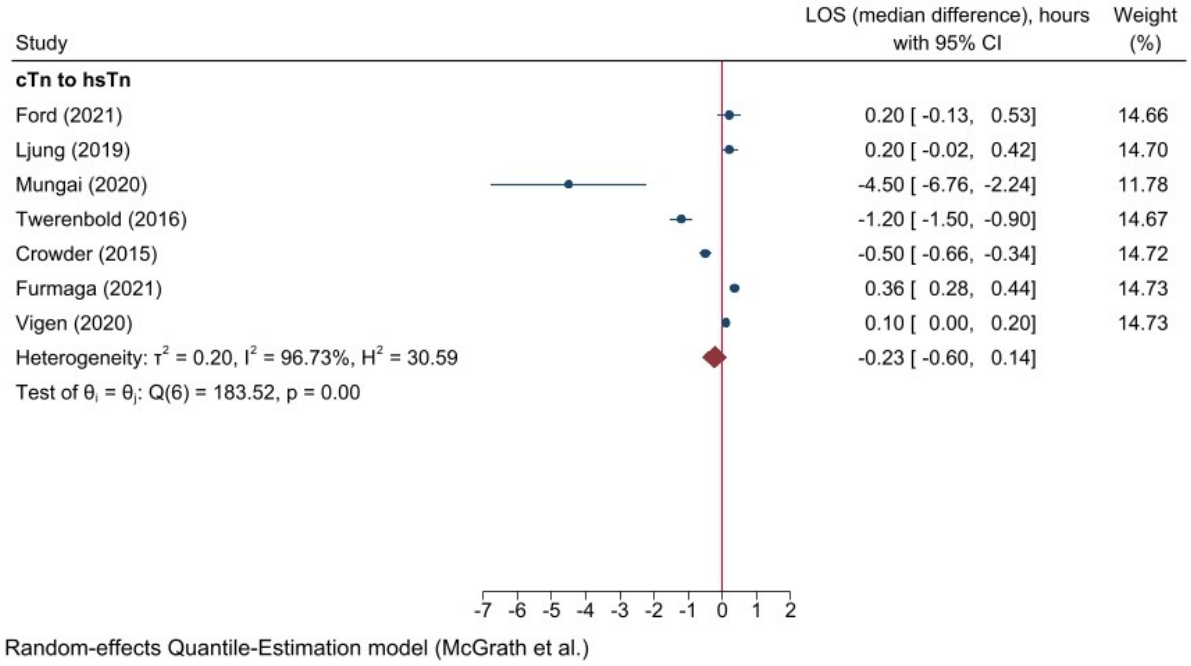
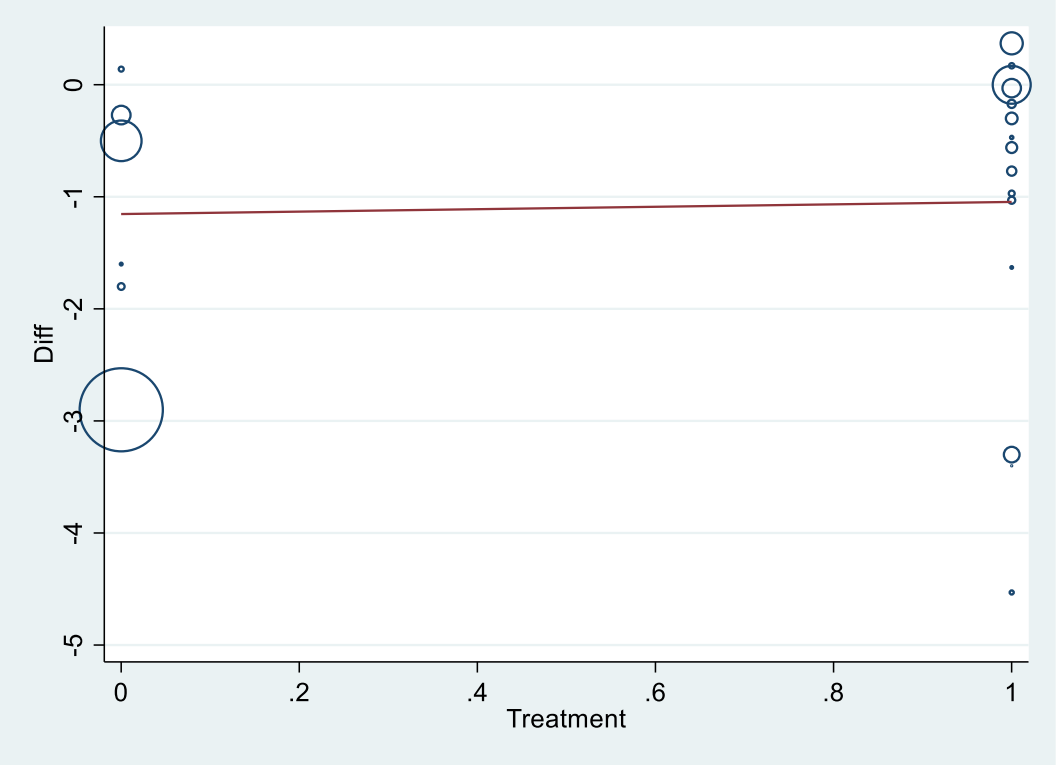
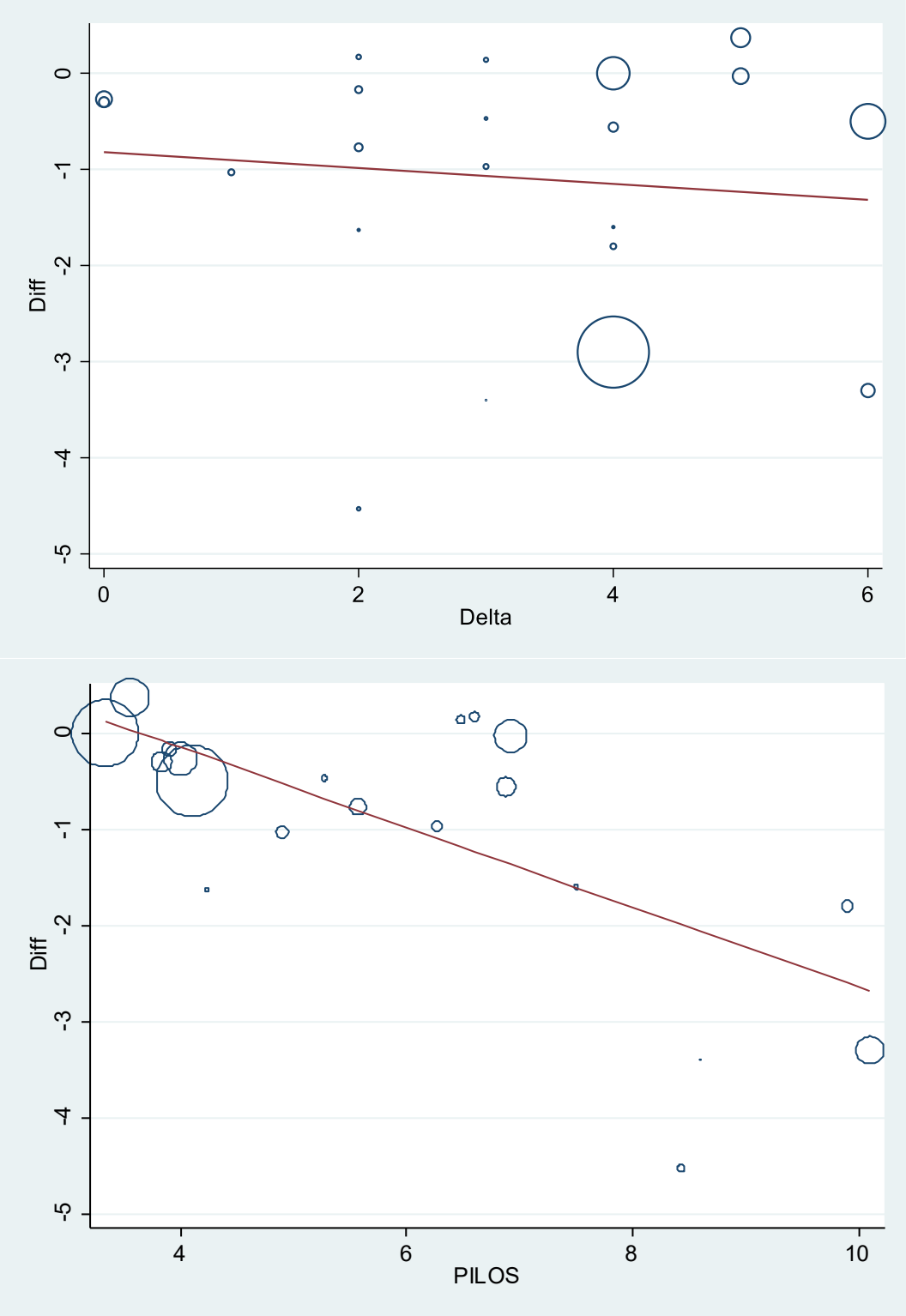


Figure 2.6 Meta-regression results examining effect of various parameters on emergency department length of stay.

Parameter	Univariate regression	Bi-variate regression
Use of hs-Tn (yes/no) "Treatment"	Beta=0.11; p=0.87	Beta=0.06; p=0.93 (with Delta); Beta=-0.47; p=0.38 (with PILOS)
Change in Troponin interval (hours) "Delta"	Beta=0.18; p=0.65	Beta=-0.08; p=0.67 (with hs-Tn) Beta=0.13; p=0.36 (with PILOS)
Pre-intervention LOS (hours) "PILOS"	Beta=-0.41; p=0.001	Beta=-0.45; p=0.001 (with Delta) Beta=-0.43; p=0.001 (with hs-Tn)





Notes: Delta = change in troponin interval (hours); Treatment = high sensitivity troponin (yes/no); PILOS = pre-intervention length of stay (hours)

Chapter Two References

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Chapter 3: Accelerated Diagnostic Protocol Cohort

Introduction

Chest pain is the second most common emergency department (ED) presenting complaint in Canada[1]. It is associated with important practice variation, high cost of investigation[2,3], frequent consultation, high proportions of admission to hospital[4,5], and a high rate of seven-day ED relapse requiring hospital admission[6]. Cardiac biomarkers, accelerated diagnostic protocols (ADP), and scoring systems have gained attention as strategies to reliably exclude acute coronary syndrome (ACS) at the same time as demonstrating safety using 30-day major adverse cardiac events (MACE)[7] outcomes.

Plasma cardiac troponins require time to accumulate to a detectable level after cardiac muscle necrosis. To accommodate for this rise, most acute chest pain guidelines have recommended measuring a repeat troponin level several hours after the initial test. Assessment of chest pain with a conventional troponin (cTn) historically required at least a 6-hour serial measurement to have adequate sensitivity as a rule-out strategy for ACS. Given that the remainder of the ED workup for chest pain may take approximately 1-2 hours, the 6-hour serial troponin has been identified as one cause of prolonged ED LOS[7-9]. Furthermore, these patients waiting for a 6-hour repeat Tn measure are often held in monitored beds, another limited commodity in the ED.

Over the past two decades there have been advances in cardiac biomarker assays. Development of higher sensitivity troponin assays led to improved sensitivity for measurement of lower troponin concentrations[8]. This lower detection threshold was combined with clinical decision rules to evaluate the safety of accelerated diagnostic protocols (ADP), with shorter serial measurement intervals. The HEART pathway is one such ADP and has particular

importance for ED use, as it was validated with an ED population[9]. The original HEART study used a detection threshold of 0.04 ug/L and was able to establish the safety of a 3-hour serial measurement to detect MACE with acceptable negative predictive value for low-risk patients (HEART score 0-3). Consequently, the 2015 American Heart Association guidelines endorsed the use of this accelerated protocol[10].

The effect of an ADP for chest pain on ED patient throughput has been inadequately studied, especially in the Canadian context. The objective of this study was to assess the impact of the shortened serial troponin times after the implementation of an ADP on ED length of stay, consultation rates, and patient outcomes.

Methods

Ethics: The study protocol and materials were approved by the University of Alberta Human Research Ethics Board, with a waiver of individual informed consent (Reference ID: Pro00096932). Written informed consent was not obtained from any patient or physician due to minimal risk associated with accessing the administrative database. Operational and administrative approvals were provided from Alberta Health Services (AHS) and a data sharing agreement was signed. The clinicians practicing during the study periods were unaware of the study at the time of data collection.

Setting: The Royal Alexandra Hospital (RAH) is a tertiary care, inner-city referral centre in Edmonton, Alberta, Canada assessing approximately 75,000 adult patients per year with an admission proportion of approximately 20%[11]. It is a teaching hospital for most resident services, including emergency medicine. The ED has 24-hour coverage with full-time emergency physicians, in-house Cardiology, and a cardiac catheterization lab. There is no Cardiac surgery

program available at the RAH for coronary artery bypass surgeries; however, another hospital with these capabilities is 6 km away.

Pathways: The RAH has experienced several changes in its troponin reporting and accompanying chest pain protocols; these changes have reflected the ongoing evolution of published recommendations for investigating patients presenting with cardiac chest pain. From January 14, 2017, to January 14, 2018, the RAH used the Beckman AccuTnI+3 conventional troponin I assay. The detection limit was set at 0.10 ug/L and the decision threshold set at 0.15 ug/L with 6-hour delta serial measurement interval. From January 15, 2018, to November 8, 2020, RAH kept the same assay but lowered the detection limit and decision threshold to the manufacturer recommended 99th percentile upper limit of 0.04 ug/L with a 3-hour delta serial measurement interval in conjunction with the HEART score. Assay precision at 0.04 ug/L was less than a coefficient of variation (CV) of 10%. The new algorithm was developed by integrating the original HEART pathway[9] and the AHA ACS Guidelines[10]. Prior to the introduction of the lower decision threshold, ED physicians at the RAH site were provided with education on the safety of the accelerated chest pain protocols and encouraged to use 3-hour serial measurements for patients with low-risk pre-test probability (HEART 0-3). Patients with a HEART score of 3 or less could have ACS ruled out at three hours. Patients with HEART score of >3 often had a serial 6-hour troponin assessed prior to discharge or cardiology consultation. These protocols are illustrated for reference in Figure 3.1 (modified from Mahler et al[15]). HEART scores of 0-3 are considered low risk, 4-6 intermediate risk, and 7 or above are high risk for MACE over the next 5 weeks.

Design: This is a retrospective cohort study of all adults (≥ 18 years) with a chief complaint of chest pain of cardiac origin. The classification and triaging of presenting complaints

are based on the Canadian Emergency Department Information System (CEDIS)[12] chief complaint list. The Canadian Triage and Acuity Scale (CTAS) is universally used in Canadian EDs and stratifies patients into 5-levels based on acuity, with a score of 1 being the most acute. In this study, patient enrollment was restricted to those with chest pain of cardiac origin and a CTAS score of 2 or 3 between January 14, 2017, and January 15, 2019, to explore the data one year before and after the implementation of a 3-hour cTnI cut-point. Only first index visits were included in cases of patients with multiple ED visits. Any patients with signs of ST-segment elevation myocardial infarction (STEMI) on their initial ECG were excluded. Patients were required to be registered with Alberta Health Care Insurance Plan (AHCIP) for inclusion.

Data sources: We surveyed eight databases within the population-based linked health administrative data from Alberta Health Services (AHS). All datasets are maintained and updated in the AHS Enterprise Data Warehouse.

For greater clarity, we used the National Ambulatory Care Reporting System (NACRS; which captures all visits to any ED in Alberta with record of up to 10 diagnostic fields using the *International Classification of Disease, 10th Revision, Canadian Enhancement* [ICD-10-CA] diagnoses per visit), the Emergency Department Information Tracking System (EDIS; which records presenting complaints and requests for consultation for ED visits within Edmonton), the provincial laboratory databases (which captures all general laboratory tests performed across the province), the provincial diagnostic imaging database (which captures all imaging performed across the province within AHS facilities), the Discharge Abstract Database (DAD; which captures all acute care hospital admissions and includes interventions, discharge destinations and records up to 25 diagnoses coded using ICD-10 codes), Vital Statistics (which captures date of death including out of hospital), the Provincial Registry (which captures Alberta residents with

AHCIP coverage), and the Practitioner Claims database (which captures all physician billing claims and includes up to three diagnoses recorded per visit using ICD-9 and a Scheduled of Medical Benefits [SOMB] billing code).

Outcomes: Descriptive statistics were calculated for both groups. In addition, baseline data are reported on physician initial assessment (PIA) and patient leaving without being seen (LWBS) in order to compare ED crowding metrics.

The primary outcome of this study was ED LOS. Secondary outcomes focused on several operational outcomes, including consultation proportions and disposition (i.e., admission or discharge) status. Additionally, we examined the proportion of patients experiencing MACE within 30 days of the index ED visit to evaluate patient safety. The composite MACE score is defined as all-cause death, hospitalization for heart failure, hospitalization and/or ED visit for myocardial infarction (MI) or stroke, or cardiac interventions (e.g., coronary artery bypass graft surgery [CABG], percutaneous coronary intervention [PCI]).

Patients who received troponin I testing were classified into one of three subgroups: negative, indeterminate, and high risk (Figure 3.2). To ensure patient groups were balanced with respect to baseline comorbid status, we identified comorbidities for each patient using previously validated case definitions based on ICD-10 and ICD-9 codes for all hospitalizations and ED visits in the 2 years prior to index ED visit (and including the index ED visit) and at least 2 hits in Practitioner Claims database[13]. We used this data to calculate a modified Charlson Comorbidity Index score[14]. Additional covariates included imaging received while in the ED and mode of arrival.

Statistical analysis: Descriptive data are reported using proportions, means with standard deviations (SD), or medians with interquartile range (IQR), as appropriate. Baseline

characteristics were compared between groups using Pearson's χ^2 test for categorical variables, Student *t* test for normally distributed variables, and Mann-Whitney test for non-normally distributed continuous variables. Quantile regression was used to directly estimate the difference in medians between groups and to provide 95% CIs. Due to the differences between non-parametric testing, which relies on data ranking, and quantile regression, which directly estimates the difference of medians between groups, subtle differences in reported significance are possible. We elected to report both measures and only consider results significant if there was concordance. Multivariable stepwise Cox proportional hazard regression was used to quantify the relationship between periods (pre-ADP period as reference category) and MACE, adjusting for age, sex, and covariates that were statistically significant after using stepwise selection (entry criterion $p<0.2$, retention criterion $p<0.05$). Adjusted hazard ratios (aHRs) with 95% confidence intervals (CI) are reported.. Statistical significance for our primary outcome was set at $p<0.05$. For all other tests, significance was set at $p < 0.001$ due to the multiple tests performed. All analyses were conducted using SAS, version 9.4 (SAS Institute, Cary, NC, USA).

Results

Demographics: The characteristics of the patient presentations are reported in Table 3.1. There were a total of 3133 patient interactions included in the study period, with 1531 (49%) in the pre-ADP group and 1602 (51%) in the post-ADP group. The median age was 58 (IQR: 46, 71) and 57.1% of the included patients were male. There were no statistically significant differences in patient demographics, timing, or severity of presentation between the groups. Additionally, patients were balanced with respect to comorbidities, with a median score of one on the Charlson comorbidity index. The proportion of patients LWBS was temporally stable,

3.6% pre-ADP and 3.2% post (p=0.53). Finally, PIA times (60 pre vs. 64 minutes post; p = 0.10) were similar between the time periods.

Investigations: There were slightly different proportion of troponin I orders between groups (Table 3.2). In the pre-ADP cohort, 9.7% had no troponin drawn, 47.1% had a single troponin, and 41.3% had two troponins. The ADP cohort had 8.1% with no troponin, 51.8% with a single troponin, and 38% with two. Before the introduction of the ADP 47.3% of patients were stratified as negative; post-ADP, this number was stable at 47.5%. There were differences between the previously described categories of indeterminate, and high-risk. Those stratified as indeterminate decreased from 41.9% to 36.5% (p=0.003), while those stratified as high risk increased significantly from 10.9% to 15.4% (p<0.001). There were no significant differences between the proportion of patients undergoing CT or VQ scans to evaluate for pulmonary embolism and other causes of chest pain. There was no increase in the number of patients receiving specialist consultation in the ED (36.1% before and 33.8% after; p=0.17).

Outcomes: As displayed in Table 3.3, the final patient dispositions were similar between groups. Overall, most patients (71.1%) were discharged home. There was a non-significant decrease (p = 0.074; Table 3.3) in the median ED LOS in the post-ADP group (Median difference = 30 minutes; 95% CI: 11.2, 48.8). It is worth noting that despite the non-significant p value, the reported 95% confidence interval does not cross zero; this is due to the different statistical tests employed, as previously outlined.. Among patients who were discharged, there was a significant decrease (p=0.035; Table 3.3) in median LOS in the post-ADP group (Median difference = 33.5-minutes; 95% CI: 12.4, 53.6)

Safety: The 30-day clinical outcomes were similar between the groups. The MACE outcomes did not change following the implementation of an ADP (15.9% vs. 15.3%; p=0.62) (Figure 3.3).

Discussion

This retrospective study was designed to evaluate the impact of introducing an ADP on ED operational efficiency, clinical outcomes, and patient safety. The pathway employed a new conventional TnI cut-point (≤0.15 ug/L to ≤0.04 ug/L), shortened serial measurement interval (from 6 to 3 hours), and a clinical decision rule (HEART) to improve efficiency. Although many tertiary-care EDs are transitioning to high-sensitivity troponin assays, there are many Canadian EDs which still rely on conventional assays for troponin testing. Patient characteristics were similar between the identical 1-year seasonally matched study periods. Following the implementation of the ADP there was a slight increase in the proportion of patients receiving one troponin, with fewer patients receiving either zero or two troponins in the post-ADP group. This difference could be partially explained by the fact that many patients in the conventional work-up group would have their initial troponin drawn before 6 hours since the onset of chest pain had elapsed; these patients would require a second troponin by protocol. Comparatively fewer patients will have troponins drawn sooner than 3 hours after the onset of chest pain and thus a negative initial test may be sufficient to rule out ACS. In addition, a more formal chest pain protocol and education may have impacted physician behaviour.

Previous research had largely focused on ED LOS for all patients receiving troponin testing[15,16]. In our estimation, this may underestimate the impact of decreasing the serial troponin measurement interval. To account for this, we stratified patients into one of three groups: negative, indeterminate, and high risk (Figure 3.2). The proportion of patients classified as

negative was stable between groups while the proportion of those in the indeterminate or high-risk groups changed (Table 3.2). In some ways this was anticipated, as patients with chest pain and some degree of cardiac ischemia, troponin values between 0.04-0.15 ug/L would result in differential classification depending on the cohort. Conversely, patients presenting with chest pain from a non-cardiac source are likely equally and temporally represented, and thus will not have a demonstrable troponin rise even with the change in detection threshold.

Surprisingly, there was no significant reduction in median ED LOS after the change to a 3-hour serial troponin and its associated ADP. Patients in the negative group only receive a single troponin measurement and as such, their ED LOS would be unaffected by changes in repeat measurement intervals. This was borne out by our results, as the LOS was unchanged between pre and post groups (Table 3.3). All patients in the indeterminate group received serial troponin measurement. Despite a 3-hour decrease in serial troponin measurement intervals, these patients remained in ED for similar median durations before and after the introduction of an ADP. Finally in the high-risk group, there was no statistically significant difference between the ED LOS between the pre- (median 470 minutes) and post (median = 395 minutes) after the ADP was introduced ($p = 0.71$); however, variability in LOS was observed.

Evidently there is more nuance to the overall ED LOS than what is captured within the serial troponin measurement interval. Dispositional challenges may play a role in this lack of demonstrated effect; patients may require ongoing pain management, advanced imaging, arrangements for outpatient testing, or other time-consuming interventions. Additionally, lack of protocol adherence could be a contributor to the modest reductions.

The only subgroup which experienced a significant decrease in median LOS were patients who were discharged, with a 33-minute decrease (95% CI: 12.4, 53.6; $p=0.035$).

Discharged patients could theoretically come from any of the low, indeterminate, or high-risk groups. It appears that an ADP helps to streamline the discharge process in at least two ways; by decreasing serial measurement timing and by diminishing the cognitive burden of how to interpret results. Proactive physicians can be ready to execute a disposition plan as soon as the repeat troponin is reported.

Despite the increased proportion of patients in the high-risk group, the proportion of Cardiology consults remained stable between groups. Based on the data about 35% of all patients have a consultation as part of their visit; this group would likely be composed largely of a mix of the high risk and intermediate risk groups. In the post-ADP group, the increase in the high-risk group was almost exactly mirrored by a decrease in the intermediate risk group. It is reasonable to infer that clinician gestalt can identify higher risk cardiac patients (based on history or risk factors) and consult Cardiology despite potentially reassuring troponin values. If the proportion of patients presenting with concerning histories remains stable between groups, then it makes sense that the consults stay stable as well. The post-ADP group eliminates the need to apply gestalt for patients who would have had a troponin value between 0.04 ug/L-0.15 ug/L.

Re-admissions for heart failure had a non-significant relative decrease of nearly 50%. Other safety outcomes such as MACE and all-cause re-admissions within 30-days were unchanged after the ADP. This is consistent with the growing body of literature on this topic[17,18].

Strengths and Limitations

There are some limitations to our research given the retrospective design of the study; however, these system-wide changes needed to be comprehensive and hospital-based, meaning that randomization at the individual patient level was not feasible. In our defense, applying valid quality metrics, this study rates strongly for a Before-After study[19]. Due to ED crowding, there is

a possibility that wait times changed between the two periods of data collection and that this is confounding our results; however, comparing the PIA and LWBS proportions between groups is a valid surrogate. Typically, in periods of increased ED wait times, there is a corresponding increase in the number of patients who LWBS. Reassuringly, these standard ED crowding metrics (PIA and LWBS) were unchanged in the pre- and post-study periods.

Physician adherence to protocol is another area for consideration. Some physicians do not use serial troponins as recommended in all situations and this is difficult to control for. Moreover, in a retrospective study, adherence measurement is complicated by missing information. Our data are exclusively drawn from a single Canadian ED, where healthcare is administered without consideration for payment, which may limit its external validity to regions without private healthcare systems. Enrollment was limited to patients triaged with symptoms of chest pain deemed to be from cardiac origin; patients presenting with atypical chest pain may have been excluded. We assumed that the turnaround time (sample collection to result reporting) remained stable in both groups; however, we did not have data to confirm or refute this. Finally, the databases don't record detailed behavioural (e.g., smoking, vaping, and cannabis use; alcohol intake; exercise; diet, etc.), management (e.g., medication, adherence, etc.) and/or sociodemographic (e.g., race; employment; income; etc.) factors which may impact acute and longer-term health outcomes.

Notwithstanding the above concerns, we believe the large sample size, pragmatic nature, and comprehensive reporting of outcomes provides a valid assessment of the efficiency and safety of the implementation of this 3-hour approach using an ADP and a cTnI test. Moreover, the results compare favourably with a recently completed systematic review[20].

Conclusions

The implementation of an ADP for chest pain in a tertiary care Canadian ED was not associated with a significant reduction of overall ED LOS for all patients; however, there was a significant reduction amongst discharged patients. In the current era of ED-overcrowding, even modest reductions in ED LOS for frequent conditions are important contributions to improved ED throughput. This strategy also has wider applicability to sites which may not yet have access to high-sensitivity troponin assays. Conventional troponin assays are becoming increasingly rare; however, for hospitals that still use conventional assays this study provides evidence for safely switching to shorter serial troponin testing. Review of admissions, MACE outcomes and deaths, which remained the same following the protocol implementation, demonstrated the safety of this approach.

Chapter 3 Tables

Table 3.1 Characteristics of patients presenting to the emergency department with chest pain before and after the introduction of an accelerated pathway using a new troponin cut-off and three-hour serial troponin testing.

	Total N=3133	Pre N=1531	Post N=1602
Age (years)			
Median (IQR)	58 (46, 71)	59 (47, 72)	58 (46, 70)
Male sex (n {%})	1788 (57.1)	908 (59.3)	880 (54.9)
Mode of arrival (n {%})			
No ambulance	1741 (55.6)	848 (55.4)	893 (55.8)
Ambulance	1372 (43.8)	670 (43.8)	702 (43.8)
Other	18 (0.6)	12 (0.8)	6 (0.4)
CTAS score (n {%})			
2	3084 (98.4)	1508 (98.5)	1576 (98.4)
3	49 (1.6)	23 (1.5)	26 (1.6)
Time of day (n {%})			
Daytime (08:01-16:00)	1392 (44.4)	664 (43.4)	728 (45.4)
Evening (16:01-24:00)	1162 (37.1)	584 (38.1)	578 (36.1)
Early morning (00:01-08:00)	579 (18.5)	283 (18.5)	296 (18.5)
Pre-existing conditions (n {%})			
Hypertension	1676 (53.5)	817 (53.4)	859 (53.6)
CAD	1317 (42.0)	658 (43.0)	659 (41.1)
Diabetes mellitus	767 (24.5)	390 (25.5)	377 (23.5)
Atrial fibrillation	697 (22.2)	352 (23.0)	345 (21.5)
Stroke	591 (18.9)	301 (19.7)	290 (18.1)
Asthma	379 (12.1)	165 (10.8)	214 (13.4)
Heart failure	404 (12.9)	212 (13.8)	192 (12.0)
COPD	534 (17.0)	270 (17.6)	264 (16.5)
Dementia	151 (4.8)	77 (5.0)	74 (4.6)
Charlson Comorbidity Index Score			
Median (IQR)	1 (0, 2)	1 (0, 2)	1 (0, 2)

Notes: CAD = coronary artery disease; CTAS = Canadian triage and acuity scale; COPD = chronic obstructive pulmonary disease; IQR = interquartile range; n =number.

Table 3.2 Testing and outcomes of patients presenting to a high-volume urban Canadian emergency department with cardiac chest pain before and after the introduction of an accelerated pathway using a new troponin cut-off and three-hour serial troponin testing.

	Total N=3133	Pre N=1531	Post N=1602	P-value
Troponin tests (n {%})				
None	279 (8.9)	149 (9.7)	130 (8.1)	0.112
One	1551 (49.5)	721 (47.1)	830 (51.8)	0.008
Two	1241 (39.6)	633 (41.3)	608 (38.0)	0.052
≥Three	62 (1.9)	28 (1.9)	34 (2.1)	0.555
Troponin results (n {%})				
Negative	1352/2854 (47.4)	653/1382 (47.3)	699/1472 (47.5)	0.900
Indeterminate	1116/2854 (39.1)	579/1382 (41.9)	537/1472 (36.5)	0.003
High	377/2854 (13.2)	150/1382 (10.9)	227/1472 (15.4)	**<0.001**
Chest imaging (n {%})				
Chest X-Ray (CXR)	2402 (76.7)	1176 (76.8)	1226 (76.5)	0.851
Chest CT scan (CTPE)	208 (6.6)	109 (7.1)	99 (6.2)	0.291
V/Q scan	41 (1.3)	16 (1.0)	25 (1.6)	0.204
ED Consultation (n {%})				
Yes	1094 (34.9)	553 (36.1)	541 (33.8)	0.168
Number of ED consultation (Median {IQR})	1 (1, 1)	1 (1, 1)	1 (1, 1)	0.605
Consult Service (n {%})				
Cardiology	786 (71.8)	390 (70.5)	396 (73.2)	0.326
General Medicine	229 (20.9)	128 (23.1)	101 (18.7)	0.069
GP	53 (4.8)	22 (4.0)	31 (5.7)	0.225
GI	45 (4.1)	20 (3.6)	25 (4.6)	0.403
General Surgery	31 (2.7)	14 (2.5)	17 (3.1)	0.543

Notes: CTPE = computed tomography for pulmonary embolism; CXR = chest x-ray; GI = gastroenterology; GP = general practitioner; IQR = interquartile range; n = number; VQ scan = pulmonary ventilation and perfusion scan.

Table 3.3 Patient outcomes before and after the implementation of an accelerated pathway using a new troponin cut-off and three-hour serial troponin testing.

	Total N=3133	Pre N=1531	Post N=1602	P-value	Median differences with 95% CI
Disposition (n {%})					
Admitted	769 (24.5)	388 (25.3)	381 (23.8)	0.310	N/A
Discharged	2228 (71.1)	1072 (70.0)	1156 (72.2)	0.186	N/A
LWBS	106 (3.4)	55 (3.6)	51 (3.2)	0.527	N/A
LAMA	29 (0.9)	15 (1.0)	14 (0.9)	0.757	N/A
Died	1 (0.0)	1 (0.1)	0 (0.0)	N/A	N/A
ED Physician initial assessment time (median {IQR})	62 (33, 114)	60 (31, 113)	63 (34, 114)	0.102	-4.0 (-9.0 to 1.0)
ED Length of stay (median {IQR})					
Overall	383 (260, 523)	401 (261, 528)	371 (257, 513)	0.074	30.0 (11.2 to 48.8)
Negative	306 (228.5, 415)	304 (226, 420)	307 (229, 408)	0.814	-3.0 (-18.7 to 12.7)
Indeterminate	494.5 (414, 596)	502 (428, 604)	490 (406, 585)	0.090	12.0 (-5.1 to 29.1)
High	420 (250, 566)	470 (275, 604)	395 (241, 555)	0.071	74.0 (6.1 to 141.9)
Admitted	392 (234, 566)	399.5 (224.5, 778)	376 (239, 561)	0.784	23.0 (-26.7 to 72.7)
Discharged	396 (284.5, 515.5)	412 (286, 521)	378.5 (282, 509.5)	0.035	33.0 (12.4 to 53.6)
Re-admissions within 30 days (n {%}) (all-cause)	900 (28.7)	458 (29.9)	442 (27.6)	0.151	N/A
Re-admissions within 30 days (n {%}) (heart failure)	99 (3.2)	61 (4.0)	38 (2.4)	0.010	N/A
Clinical outcomes within 30 days (n {%})					
Stroke	13 (0.4)	8 (0.5)	5 (0.3)	0.360	N/A
MI	307 (9.8)	143 (9.3)	164 (10.2)	0.399	N/A
Cardiac interventions[‡]	268 (8.6)	128 (8.4)	140 (8.7)	0.705	N/A
Death	55 (1.8)	26 (1.7)	29 (1.8)	0.811	N/A
MACE[α]	489 (15.6)	244 (15.9)	245 (15.3)	0.620	N/A

Notes: CI = Confidence interval; IQR = interquartile range; LAMA = leaving against medical advice; LWBS = leaving without being seen; MACE = major adverse cardiac events; MI = myocardial infarction; N/A = Not applicable; n = number.

[‡]Cardiac interventions include coronary artery bypass graft surgery (CABG) and percutaneous coronary intervention (PCI).

[α]MACE is defined as a composite of all-cause death, hospitalization for heart failure, hospitalization or/and ED visit for stroke or MI, or cardiac interventions.

Chapter 3 Figures:

Figure 3.1 Pathway illustrating modified HEART algorithm distributed to emergency department physicians at the Royal Alexandra Hospital.

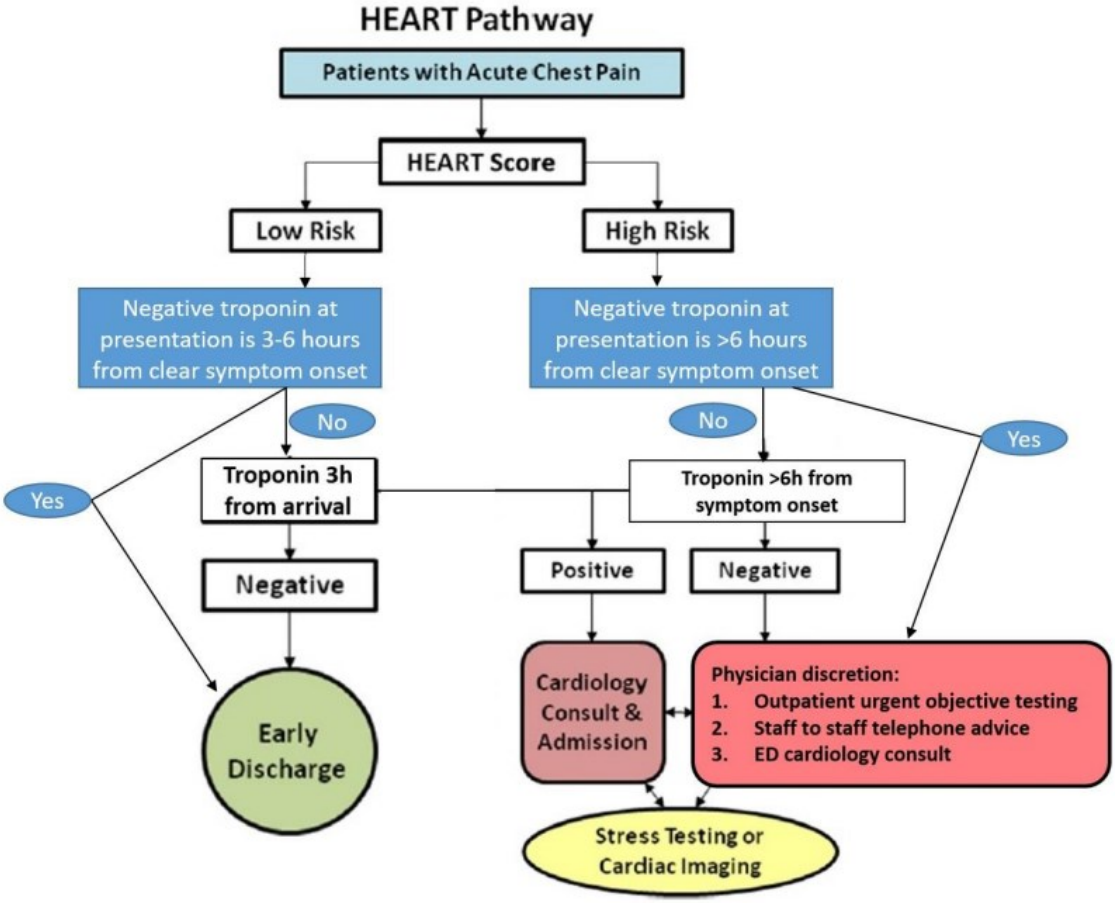


Figure 3.2 Royal Alexandra Hospital chest pain protocols before-and-after introduction of accelerated diagnostic protocol.

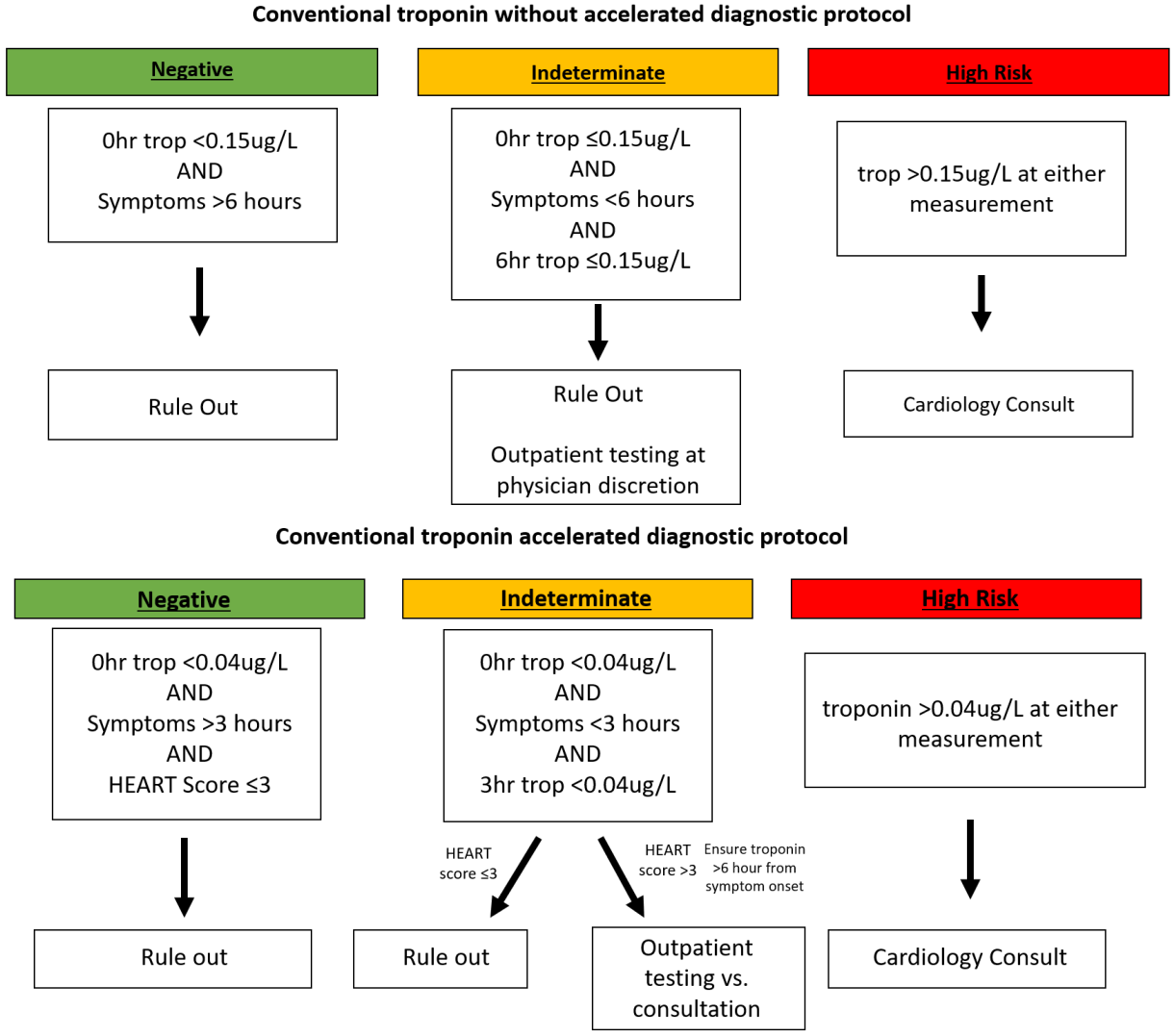
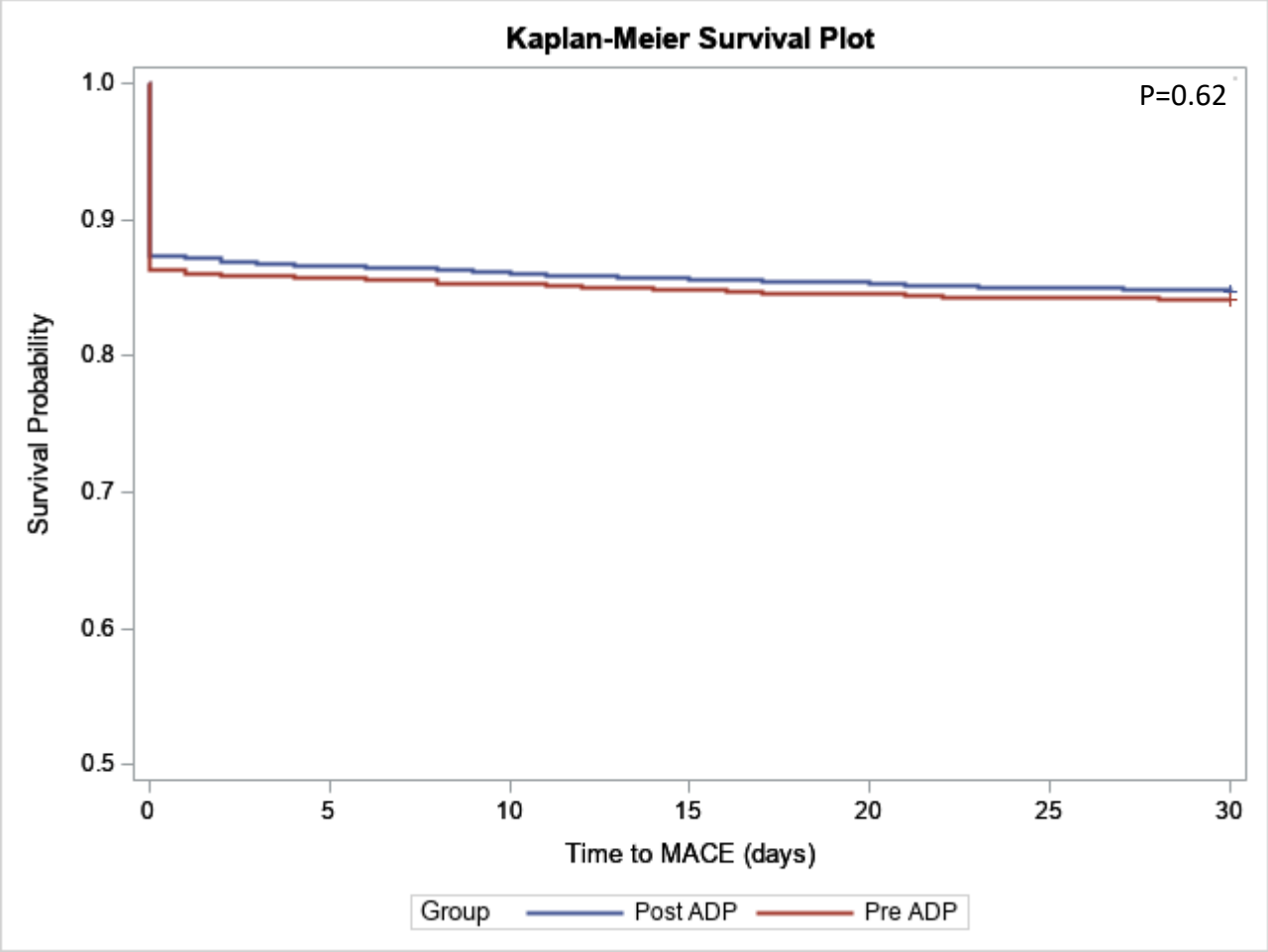


Figure 3.3 Kaplan-Meier survival curves for MACE in patients presenting to a high-volume urban Canadian emergency department with cardiac chest pain before and after the introduction of an accelerated pathway using a new troponin cut-off and three-hour serial troponin testing.



Note: MACE = Major adverse cardiac events, indicates all-cause death, hospitalization for heart failure, hospitalization or/and ED visit for stroke or MI, or cardiac interventions.

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Chapter 4: High Sensitivity Troponin Comparative Study

Introduction

Evaluation of patients presenting with chest pain is a cornerstone of emergency department (ED) care. Chest pain is the second most common ED presenting complaint in Canada[1]. Many serious underlying medical conditions may be heralded by chest pain, so most of these patients undergo thorough ED assessment and testing. Standard investigations include an electrocardiogram (ECG), chest radiograph, complete blood count and electrolytes, cardiac biomarkers (i.e., troponins {Tn}), plus or minus special investigations (e.g., D-dimer, advanced imaging). One of the mainstays of assessment is serial measurement of cardiac biomarkers. For example, Tn, accumulates in blood after cardiac muscle necrosis and rising levels act as a surrogate marker of acute myocardial infarction (AMI) and acute coronary syndromes (ACS).

Conventional Tn (cTn) detection thresholds vary in analytical sensitivity and precision at lower concentrations, with approximate ranges from 40-100 ng/L[2]. High sensitivity Tn (hs-Tn) assays have further improved detection. For example, the Beckman hs-TnI used in our study has a detection threshold of 3 ng/L. This reduction has led to decreased time between repeat troponin levels from the recommended 6 hours associated with a cTn to as low as 1 hour with some hs-Tn assays[3]. Clearly, this represents an opportunity to improve ED throughput for patients presenting with chest pain. More efficient and timely care of these patients has the potential to decrease ED length of stay (LOS), cost, and ED overcrowding. Initial studies on hs-Tn usage were characterized by confirmation of adequate sensitivity and appropriate safety profiles[4-6]. The encouraging results of these early studies have led to widespread adoption of hs-Tn use in EDs across the world[4-8].

There are several potential unintended consequences of increased troponin sensitivity. For example, minor Tn elevations caused by non-ACS issues may now be detected with increasing frequency[5]. In addition, such elevations may result in more consultations with Cardiologists as well as admissions. Subtle elevations warrant further testing in patients who would previously have been deemed negative using less sensitive Tn assays. It is possible that this increased test sensitivity is partly responsible for the relatively modest or negligible reductions, even increases in some cases, in ED LOS reported after transitioning from cTn to hs-Tn assays[7-13]. For example, in a recent systematic review of chest pain protocols, the median ED LOS ***increased*** in four studies after implementation of a hs-Tn assay[8-10,13]. Conversely, within a Canadian context, observational data demonstrated as small as a 30-minute reduction in total ED LOS after the transition from a 6-hour to a 2-hour protocol using a hs-TnT troponin assay[7]. As such, current literature shows differing effects on ED LOS when implementing hs-Tn testing, and more studies are needed.

Part of the challenge of implementing a new hs-Tn assay is designing an appropriate protocol to achieve an acceptable sensitivity while being sensible to clinicians. The objective of this study was to assess the impact of the introduction of a hs-TnI assay and its associated accelerated protocol on ED LOS for patients presenting with chest pain, while holding serial troponin measurement intervals constant. By reporting on ***all*** patients undergoing troponin testing, there is a possibility of underestimating the impact of the hs-Tn for a specific subgroup of patients with chest pain. Consequently, we sought to analyze patients in subgroups which were predicted to benefit variably from the lower detection threshold of a hs-Tn.

Methods

Ethics: The study was approved by the University of Alberta Health Research Ethics Board (Reference ID: Pro00096932) at the University of Alberta, in Edmonton, Alberta, Canada. The project was assessed as minimal risk and approved to access electronic medical records from administrative database. Written informed consent was not obtained from any patient or physician participants. Operational and administrative approvals were provided by Alberta Health Services (AHS) and a data sharing agreement was signed. The clinicians practicing during the study periods were unaware of the study at the time of data collection.

Setting: The Royal Alexandra Hospital (RAH) is an academic tertiary-care hospital in Edmonton, Alberta, Canada. The RAH is a referral centre for cardiology and assesses approximately 73,000 adult patients per year with an admission proportion of 18%[13]. This hospital is considered an inner-city hospital and many of their patients struggle with homelessness, addictions, and poverty. The ED is staffed with full-time emergency physicians, and functions as a teaching site for emergency and other resident services. The hospital has Cardiology consultative services and a cardiac catheterization lab. There is no Cardiac surgery program available at the RAH for coronary artery bypass surgeries; however, another hospital with these capabilities is 6 km away.

Assays and Pathways: The RAH operated with different chest pain protocols based on troponin laboratory reporting between 2019 and 2021. From November 9, 2019, to November 8, 2020, the RAH used the Beckman AccuTnI+3 assay (conventional TnI) with a limit of detection of 0.04 ug/L. Emergency physicians at the RAH site were provided with education on the safety of accelerated chest pain protocols and encouraged to use a 3-hour serial measurement, in conjunction with the HEART score to help risk stratify. From November 9, 2020, to November 9, 2021, the RAH switched to the Beckman hs-TnI assay. The limit of detection was set at 3 ng/L

and the 99th percentile upper limit was 20 ng/L. A coefficient of variation (CV) of <10% was achieved at the 99th percentile[14]. No sex specific cutoffs were used for hsTnI. The protocol for each respective period is illustrated in Figure 4.1.

Implementation Strategy: Prior to the implementation of the hs-TnI protocol, extensive efforts were made to educate Emergency, Internal Medicine, and Cardiology clinicians across the zone. Prior to the implementation date, a 10-minute video was produced that detailed the new protocol and a "Survival Guide" was developed by a multi-disciplinary team of Laboratory Medicine leaders and Emergency Medicine, Internal Medicine, and Cardiology clinician-scientists. A paper-based version of the protocol was distributed to the EDs and the clinical group received an in-service from the two lead ED clinicians (BHR; SD). Immediately prior to the implementation, a Laboratory Bulletin was sent through Medical Affairs secure email channels to remind staff of the pending changes. All changes were reported using the new assay without any run-in period.

Design: We conducted a retrospective cohort study of all adults (≥ 18 years) with a primary presenting complaint of chest pain of cardiac origin from the Canadian Emergency Department Information System (CEDIS) presenting complaints list[16]. The majority of EDs in Canada employ the 5-level Canadian Triage and Acuity Scale [CTAS]. In this study, patient enrollment was restricted to those with chest pain of cardiac origin and a CTAS score of 2 or 3 between November 8, 2019, and November 9, 2021. When patients had multiple ED visits, we included only their first index visit. We excluded patients with a clear diagnosis of ST-segment elevation myocardial infarction (STEMI). Those who died during ED transport or upon arrival, and non-Alberta residents or those who were not registered with the Alberta Health Care Insurance Plan (AHCIP) were also excluded.

Data sources: Population-based linked health administrative data from Alberta was obtained. Eight databases were used to identify the final study cohort. All datasets are maintained and updated in the Alberta Health Services (AHS) Enterprise Data Warehouse.

We used the National Ambulatory Care Reporting System (NACRS; which captures all visits to any ED in Alberta and records up to 10 diagnostic fields using the *International Classification of Disease, 10th Revision, Canadian Enhancement* [ICD-10-CA] diagnoses per visit), the Emergency Department Information Tracking System (EDIS; which captures all ED visits in Edmonton and records presenting complaints and consultation services), the provincial laboratory databases (which captures all general laboratory tests performed across the province), the provincial diagnostic imaging database (which captures all imaging performed across the province within AHS facilities), the Discharge Abstract Database (DAD; which captures all acute care hospital admissions and includes interventions, discharge destinations and records up to 25 diagnoses coded with ICD-10), Vital Statistics (which captures date of death including out of hospital), the Provincial Registry (which captures Alberta residents with AHCIP coverage), and the Practitioner Claims database (which captures all physician billing claims and includes up to three diagnoses recorded per visit using ICD-9 and a Scheduled of Medical Benefits [SOMB] billing code).

Outcomes: Descriptive statistics were calculated for both groups. In addition, baseline data are reported on physician initial assessment (PIA) and patients leaving without being seen (LWBS) in order to compare ED crowding metrics.

Our primary outcome was ED LOS. Secondary outcomes included consultation proportions, disposition status (i.e., admission or discharge), and Major Adverse Cardiac Events (MACE), defined as a composite of all-cause death, hospitalization for heart failure,

hospitalization and/or ED visit for myocardial infarction (MI) or stroke, or cardiac interventions (e.g., coronary artery bypass graft surgery [CABG], percutaneous coronary intervention [PCI]) within 30 days of the index ED visit. We identified comorbidities for each patient using previously validated case definitions based on ICD-10 and ICD-9 codes for all hospitalizations and ED visits in the 2 years prior to index ED visit (and including index ED visit) and at least 2 hits in Practitioner Claims database[17]. Other non-clinical covariates included the arrival by EMS, a modified Charlson Comorbidity Index (CCI) score[18], and imaging received during their ED visit. Patients who had at least one troponin test were divided into negative, indeterminate, and positive groups based on the reference ranges (Figure 4.1). When more than two troponins were measured, we included the first two test results.

Statistical analysis: Descriptive data are reported using proportions, means with standard deviations (SD), or medians with interquartile range (IQR), as appropriate. Baseline characteristics were compared between groups using: Pearson's χ^2 test for categorical variables, Student *t* test for normally distributed variables, and Mann-Whitney test for non-normally distributed variables for continuous variables. Multivariable stepwise Cox proportional hazard regression was used to quantify the relationship between hs-TnI period (cTn period as reference category) and MACE, adjusting for age, sex, and covariates that were statistically significant after using stepwise selection (entry criterion $p<0.2$, retention criterion $p<0.05$). Adjusted hazard ratios (aHRs) with 95% confidence intervals (CI) are reported. This analysis was specifically focused on the subgroup of patients who had at least one troponin test. Finally, we used an interrupted time series analysis to determine if the level (immediate) and slope (trend) changed after the implementation of hs-TnI. Median differences with 95% CIs are reported for continuous variables. Statistical significance for our primary outcome was set at $P<0.05$. For all other tests

(except the multivariable Cox regression analysis), significance was set at $P < 0.001$ because of the multiple tests performed. All analyses were conducted using SAS, version 9.4 (SAS Institute, Cary, NC, USA).

Results

Demographics: The characteristics of the patient presentations are reported in Table 4.1. There were a total of 2640 patients who presented with chest pain included in the study period, with 1333 (50.5%) in the cTnI group and 1307 (49.5%) in the hs-TnI group. The median age of all included patients was 57 (IQR: 44, 69), with 54.8% being male. There were no differences in patient demographics, timing, or severity of presentation between the groups. Time to initial physician assessment was stable between study periods, with median times of 59 and 60 minutes, before-and-after hs-TnI introduction, respectively (median differences = -1.0 minutes; 95% CI: -6.4, 4.4).

Investigative Details: Among all patients presenting with chest pain of cardiac origin, 91.4% underwent troponin testing (Table 4.2). There were more patients having two troponins ordered after the introduction of the hs-TnI assay (44.3% versus 38.3%; p = 0.002). In the hs-TnI group, 60.1% of patients were classified as negative while 29.2% of patients were indeterminate; these changes represent significant increases and decreases (p<0.0001) from the year prior using the cTnI assay, respectively. The proportion of patients classified as high-risk remained unchanged between groups. There were no significant differences between the proportion of patients undergoing chest imaging modalities. Consultation occurred in 37.4% of patient presentations in the cTnI group and 33.8% in the hs-TnI group (p=0.06).

Primary LOS Outcomes: Overall, median ED LOS decreased significantly after the introduction of the hs-TnI; the median times were 392 minutes for the cTnI group and 371

minutes for the hs-TnI group (median difference = 21 minutes; 95% CI: 5.3, 36.7). Among patients who were discharged, there was a significant decrease in LOS by 34 minutes (95% CI: 18.1, 49.9) following the implementation of the hs-TnI assay. Those stratified as Indeterminate saw the largest decrease in LOS following the implementation of the hs-TnI assay (median difference = 100 minutes; 95% CI: 69.6, 130.1) (Table 4.3). Patients in the negative group experienced an increase in LOS (median difference = -38 minutes; -56.1, -19.9).

Secondary outcomes: As displayed in Table 4.3, the final patient dispositions were similar between groups. Overall, most patients (71.5%) were discharged home. There were no differences in discharges between the cTnI and hs-TnI groups (71.1% vs. 71.9%; p=0.65). Similar proportions of patients left without being seen (LWBS) by physicians between the study periods.

The proportion of patients who were admitted to hospital remained similar (25.1% vs 23.9%; p=0.48) following the pathway changes. The overall 30-day clinical outcomes were similar between groups. The MACE outcomes did not change following the implementation of the hs-TnI test (13.6% vs 13.1%; p=0.71). Table 4.4 illustrates the Cox regression analysis for MACE. Many conventional cardiac risk factors (e.g., age, history of coronary artery disease, diabetes) demonstrated statistically significant unadjusted hazard ratios. After adjustment in Cox regression modeling, no overall difference in MACE was noted in the hs-TnI group as compared with the cTnI group (aHR = 1.12; 95% CI: 0.90, 1.41). Our interrupted time series failed to demonstrate a significant change in MACE after the introduction of the hs-TnI (p=0.60) (Figure 4.2).

Discussion

This study was designed to evaluate the effectiveness and safety of an accelerated protocol associated with a change to a high-sensitivity troponin in an urban, high-volume

teaching ED for patients presenting with chest pain assessed to be cardiac in nature. Between the study periods, the patient populations appear not to be different and no important changes in the characteristics of patients were detected, although the chaos of a global COVID pandemic continued. There was no corresponding increase in the amount of specialist consultation. Given the oft-cited concern that clinically irrelevant troponin quantities will increase Cardiology consultations to unsustainable levels, this finding was reassuring. Additionally, the proportion of patients being discharged home from ED remained stable. Finally, the hs-TnI and associated protocol resulted in a significant reduction in overall ED LOS for all patients presenting with chest pain. The magnitude of the reduction for unstratified all-comers (21 minutes) is consistent with other reported Canadian experience[7].

There are important differences to note between the chest pain protocols. The HEART pathway, which was the basis of the accelerated diagnostic pathway in the cTnI period required calculating a HEART score for all patients. Only those with scores of three or less can technically be in the early rule out group. Additionally, the test is effectively binary: patients either have no detectable troponin, or else they have an elevated result and cardiology consultation was recommended. By comparison, the hs-TnI accelerated chest pain protocol was more nuanced. Specific guidance was provided to physicians on acceptable troponin thresholds and changes in troponin levels between serial measurements (delta). Risk stratification was only recommended for patients in the indeterminate category. The advice on stratification was similar to that of the HEART pathway, whereby a score of ≤3 would warrant outpatient stress testing and higher scores may call for Cardiology involvement. Patients with undetectable (<3ng/L) or grossly elevated (>100ng/L) troponin results with symptoms greater than 3 hours since onset were managed very similarly to the cTnI protocol.

The low-risk or rule-out group experienced an increased LOS after transition to the hs-TnI protocol. This is likely driven by differences in the retrospective classification rather than true clinical differences. In both pre- and post- groups, patients with an initially undetectable troponin and symptoms over three hours could be ruled as negative or low risk; however, in the hs-TnI group patients undergoing serial troponin testing could also be classified as low risk if their troponin was <20ng/L and they had a delta change of <5ng/L. We suggest this difference also accounts for the increased proportion of patients in the negative group of the hs-TnI protocol.

The Indeterminate group is perhaps the most directly comparable. These were patients not meeting criteria for rule-out or rule-in cardiac damage and thus requiring serial measurements. An impressive 100-minute median reduction in ED LOS (95% CI: 69.9, 130.1; $p<0.0001$) was demonstrated with the adoption of the hs-TnI assay and protocol for this group. Given the consistent 3-hour serial interval, this reduction is more difficult to explain. A possible explanation is increasing physician comfort with trending troponin measurements. Troponin pathways were relatively novel in the ED setting in 2015[19], compared to more recent years in our ED setting where they have become much more common; from nurses becoming comfortable drawing repeat measurements at the appropriate intervals, to electronic medical systems enabling ordering from anywhere in the department. Certainly, there is some component of lack of protocol adherence; physicians who do not order a repeat troponin despite the initial value being >3ng/L. This would cause a patient to be analyzed in the Indeterminate group despite potentially being discharged after a single troponin. Lack of protocol compliance has been documented in similar studies[7]. To account for this, we also analyzed the subgroup of discharged patients who received 2 troponins. There was still a decrease in median LOS from 476.5 to 410 minutes

($p<0.0001$), though by definition this can include patients in any of the three groups from the hs-TnI protocol.

The stable proportions of clinical outcomes across the groups are consistent with other reported literature, including both observational[7,8] and randomized[20] clinical trials. The 30-day all cause mortality was 1.5% which was comparable to other Canadian studies[7]. The interrupted time series illustrates a stable MACE across both protocols which is reassuring and suggests the strategy is safe.

Strengths and Limitations

There are some limitations to this research that warrant discussion. The study design was observational rather than randomized; however, these protocol changes were mandated by the health authority at a regional and hospital level, meaning that randomization at the individual patient level was not feasible. In our defense, applying valid quality metrics, this study rates strongly for a Before-After study[21]. All data were taken from a Canadian health care system, where services are available without charge to all citizens who are registered, which may limit its external validity to other healthcare regions. Enrollment was restricted to patients triaged with symptoms of chest pain of cardiac origin; those presenting who described their chest pain without specific classic features may have been excluded. Some laboratory samples do undergo hemolysis prior to lab analysis and thus need to be redrawn; this granularity was not captured in our administrative data. This protocol was implemented during the severe respiratory distress syndrome coronavirus-2 (SARS-CoV-2 or COVID-19) pandemic, and it was difficult to control for the impact of the pandemic on patient presentations (e.g., delays, volumes, co-infection, etc.) and operational issues. COVID was first detected within Alberta during March 2020 and there were significant changes to patient volumes and ED functioning with actual case volumes

remaining low until November 2020[22]. Anecdotally, during the period from November 2020 to January 2021, the healthcare system was under significant strain and wait times were generally longer for all presentations. Available data from this period is reflective of this, demonstrating a decrease in overall daily patient volumes beginning in January of 2020 followed by a relative increase in the proportion of higher acuity patients as well as patients requiring admission (Figure 4.3)[15]. Additionally, there was no washout period between the two protocols, and it is possible that physicians took some time to become comfortable with the new protocols. The finding that some included patients were referred to non-cardiac services (e.g., gastroenterology) may surprise readers; however, their presentations were deemed sufficiently suspicious by ED triage nurses that cardiac ischemia needed to be ruled out before referral. Finally, the databases don't record detailed behavioural (e.g., smoking, vaping, and cannabis use; alcohol intake; exercise; diet; etc.), management (e.g., medication, adherence, etc.) and/or sociodemographic (e.g., race; employment; income; etc.) factors which may impact acute and longer-term health outcomes.

Notwithstanding the above concerns, we believe the large sample size, pragmatic nature, and comprehensive reporting of outcomes provides a valid assessment of the efficiency and safety of the implementation of this approach. Moreover, the results compare favourably with the remainder of the thesis.

Conclusions

The implementation of an accelerated CP protocol using a hs-TnI assay in a tertiary care Canadian ED was associated with a surprisingly modest reduction of LOS for all patients; however, this reduction was substantial for patients undergoing serial testing. Review of admissions, MACE outcomes and deaths, which remained the same following the protocol

implementation, demonstrated the safety of this approach. Further research on protocol adherence and avoidance of troponin testing in patients with very low risk chest pain of suspected cardiac origin remains necessary. Emergency departments with prolonged assessments for chest pain should consider implementing similar approaches.

Chapter 4 Tables

Table 4.1 Characteristics of patients presenting to the emergency department with chest pain before and after the introduction of an accelerated pathway using a high-sensitivity cardiac troponin assay and a 3-hour serial troponin interval.

	Total N=2640	TnI N=1333	hs-TnI N=1307
Age (years)			
Median (IQR)	57 (44, 69)	58 (44, 70)	56 (43, 68)
Male sex (n {%})	1448 (54.8)	700 (52.5)	748 (57.2)
Mode of arrival (n {%})			
No ambulance	1463 (55.4)	731 (54.8)	732 (56.0)
Ground ambulance	1174 (44.5)	600 (45.0)	574 (43.9)
Air ambulance	3 (0.1)	2 (0.2)	1 (0.1)
CTAS score (n {%})			
2	2612 (98.9)	1316 (98.7)	1296 (99.2)
3	28 (1.1)	17 (1.3)	11 (0.8)
Time of day (n {%})			
Daytime (08:01-16:00)	1198 (45.4)	592 (44.4)	606 (46.4)
Evening (16:01-24:00)	934 (35.4)	489 (36.7)	445 (34.0)
Early morning (00:01-08:00)	508 (19.2)	252 (18.9)	256 (19.6)
Pre-existing conditions (n {%})			
Hypertension	1257 (47.6)	658 (49.4)	599 (45.8)
CAD	982 (37.2)	519 (38.9)	463 (35.4)
Diabetes mellitus	656 (24.8)	356 (26.7)	300 (23.0)
Atrial fibrillation	594 (22.5)	299 (22.4)	295 (22.6)
Stroke	477 (18.1)	232 (17.4)	245 (18.7)
Asthma	322 (12.2)	172 (12.9)	150 (11.5)
Heart failure	312 (11.8)	158 (11.9)	154 (11.8)
COPD	353 (13.4)	189 (14.2)	164 (12.5)
Dementia	101 (3.8)	49 (3.7)	52 (4.0)
Charlson Comorbidity Index Score			
Median (IQR)	1 (0, 2)	1 (0, 2)	0 (0, 2)

Notes: CAD = coronary artery disease; CTAS = Canadian triage and acuity scale; TnI = conventional troponin I assay; COPD = chronic obstructive pulmonary disease; hs-TnI = high sensitivity troponin I assay; IQR = interquartile range; n = number.

Table 4.2 Testing and outcomes of patients presenting to a high-volume urban Canadian emergency department with cardiac chest pain before and after the introduction of an accelerated pathway using a high-sensitivity cardiac troponin assay and a 3-hour serial troponin interval.

	Total N=2640	TnI N=1333	hs-TnI N=1307	P-value
Troponin tests (n {%})				**0.0034**
None	228 (8.6)	120 (9.0)	108 (8.3)	0.5
One	1275 (48.3)	669 (50.2)	606 (46.4)	0.05
Two	1090 (41.3)	511 (38.3)	579 (44.3)	**0.002**
≥Three	47 (1.8)	33 (2.5)	14 (1.1)	**0.006**
Troponin results (n {%})				
Negative	1302/2412 (54.0)	581/1213 (47.9)	721/1199 (60.1)	**<0.0001**
Indeterminate	826/2412 (34.3)	476/1213 (39.2)	350/1199 (29.2)	**<0.0001**
Positive	284/2412 (11.8)	156/1213 (12.9)	128/1199 (10.7)	0.0960
Chest imaging (n {%})				
Chest X-Ray (CXR)	2080 (78.8)	1041 (78.1)	1039 (79.5)	0.3788
Chest CT scan (CTPE)	263 (10.0)	129 (9.7)	134 (10.3)	0.6218
V/Q scan	39 (1.5)	20 (1.5)	19 (1.5)	0.9208
ED Consultation (n {%})				
Yes	940 (35.6)	498 (37.4)	442 (33.8)	0.0574
Number of ED consultation (Median {IQR})	1 (1, 1)	1 (1, 1)	1 (1, 1)	0.0969
Consult Service (n {%})				
Cardiology	633 (67.3)	332 (66.7)	301 (68.1)	0.6401
General Medicine	229 (24.4)	121 (24.3)	108 (24.4)	0.9610
GI	48 (5.1)	20 (4.0)	28 (6.3)	0.1070
GP	46 (4.9)	24 (4.8)	22 (5.0)	0.9107
General Surgery	29 (3.1)	14 (2.8)	15 (3.4)	0.6063

Notes: TnI = conventional troponin I assay; CTPE = computed tomography for pulmonary embolism; CXR = chest x-ray; GI = gastroenterology; GP = general practitioner; hs-TnI = high sensitivity troponin I assay; IQR = interquartile range; n = number; VQ scan = pulmonary ventilation and perfusion scan.

Table 4.3 Patient outcomes before and after the implementation of an accelerated pathway using a high-sensitivity troponin assay and a 3-hour serial troponin interval.

		Total N=2640	TnI N=1333	Hs-TnI N=1307	P-value	Median differences with 95% CI
Disposition (n {%})						
	Admitted	646 (24.5)	334 (25.1)	312 (23.9)	0.479	N/A
	Discharged	1888 (71.5)	948 (71.1)	940 (71.9)	0.648	N/A
	LWBS	59 (2.2)	26 (2.0)	33 (2.5)	0.318	N/A
	LAMA	46 (1.7)	25 (1.9)	21 (1.6)	0.598	N/A
	Died	1 (0.0)	0 (0.0)	1 (0.1)	N/A	N/A
ED PIA (median {IQR})		60 (31, 103)	59 (31, 100)	60 (32, 108)	0.340	-1.0 (-6.4 to 4.4)
ED LOS (median {IQR})	**Overall**	379 (277, 512)	392 (277, 525)	371 (276, 490)	0.0198	21.0 (5.3 to 36.7)
	Negative	359.5 (277, 463)	336 (249, 444)	374 (305, 475)	**<0.0001**	-38.0 (-56.1 to -19.9)
	Indeterminate	448.5 (350, 567)	484 (391.5, 600.5)	384 (267, 537)	**<0.0001**	100 (69.9 to 130.1)
	Positive	411.5 (273.5, 561.5)	407 (246.5, 563.5)	415 (317.5, 553.5)	0.5285	-7.0 (-62.1 to 48.1)
	Discharged	378 (284, 491)	397.5 (291.5, 518.5)	363.0 (281.5, 462.5)	**<0.0001**	34.0 (18.1 to 49.9)
	Discharged (repeat tests)	439 (365, 549)	476.5 (390, 574.5)	410 (352, 504)	**<0.0001**	66.0 (43.5 to 88.5)
Re-admissions within 30 days (n {%}) (all-cause)		772 (29.2)	407 (30.5)	365 (27.9)	0.1411	N/A
Re-admissions within 30 days (n {%}) (heart failure)		75 (2.8)	40 (3.0)	35 (2.7)	0.6176	N/A
Clinical outcomes within 30 days (n {%})						
	Stroke	8 (0.3)	5 (0.4)	3 (0.2)	0.4963	N/A
	MI	202 (7.7)	106 (8.0)	96 (7.3)	0.5575	N/A
	Cardiac interventions‡	188 (7.1)	92 (6.9)	96 (7.3)	0.6579	N/A
	Death	39 (1.5)	17 (1.3)	22 (1.7)	0.3851	N/A
	MACE$^{\alpha}$	352 (13.3)	181 (13.6)	171 (13.1)	0.7083	N/A

Notes: TnI = conventional troponin I assay; hs-TnI = high sensitivity troponin; IQR = interquartile range; LAMA = leaving against medical advice; LOS = length of stay; LWBS = leaving without being seen; MACE = major adverse cardiac events; MI = myocardial infarction; N/A = Not applicable; PIA =-Physician initial assessment.

‡Cardiac interventions include coronary artery bypass graft surgery (CABG) and percutaneous coronary intervention (PCI).

$^{\alpha}$MACE is defined as a composite of all-cause death, hospitalization for heart failure, hospitalization or/and ED visit for stroke or MI, or cardiac interventions.

Table 4.4 Major adverse cardiac events (MACE) outcomes of Canadian emergency department with chest pain before and after the introduction of an accelerated pathway using a high-sensitivity cardiac troponin assay and a 3-hour serial troponin interval.

Variable	Unadjusted HR (95% CI)	p-value	aHR (95% CI)*	p-value
Age				
≤45	Ref		Ref	
46-64	4.24 (2.55 - 7.07)	<0.0001	1.99 (1.18 - 3.36)	**0.0094**
≥65	8.22 (5.00 - 13.5)	<0.0001	2.31 (1.38 - 3.87)	**0.0015**
Male sex	1.52 (1.20 - 1.92)	0.0005	1.10 (0.86 - 1.40)	0.4464
EMS	2.51 (1.98 - 3.18)	<0.0001	-	-
Hypertension	2.75 (2.15 - 3.53)	<0.0001	-	-
CAD	8.88 (6.57 - 12.0)	<0.0001	2.64 (1.90 - 3.68)	**<0.0001**
Diabetes	2.33 (1.86 - 2.91)	<0.0001	1.34 (1.06 - 1.70)	**0.0132**
AFIB	1.72 (1.36 - 2.18)	<0.0001	0.75 (0.58 - 0.95)	**0.0199**
Stroke	1.60 (1.24 - 2.06)	0.0003	-	-
Asthma	0.91 (0.64 - 1.30)	0.6125	-	-
HF	4.10 (3.24 - 5.18)	<0.0001	1.69 (1.31 - 2.18)	**<0.0001**
COPD	1.37 (1.03 - 1.84)	0.0336	-	-
Dementia	1.36 (0.82 - 2.24)	0.2341	-	-
Charlson score	1.21 (1.17 - 1.26)	<0.0001	-	-
Troponin test results				
Negative	Ref		Ref	
Indeterminate	1.83 (1.30 - 2.59)	0.0006	1.04 (0.73 - 1.48)	0.8348
Positive	16.5 (12.2 - 22.1)	<0.0001	5.28 (3.83 - 7.29)	**<0.0001**
CT scan	0.71 (0.47 - 1.08)	0.1109	0.55 (0.36 - 0.84)	**0.0052**
Consultation	15.6 (10.9 - 22.4)	<0.0001	6.09 (4.12 - 9.00)	**<0.0001**
Post-implementation of hs-TnI period	1.00 (0.80 - 1.25)	0.984	1.12 (0.90 - 1.41)	0.3076

Note: aHR = adjusted hazard ratio for the cox regression model; AFIB = atrial fibrillation; CAD = coronary artery disease; CI = confidence interval; COPD = chronic obstructive pulmonary disease; HF = heart failure; hs-TnI = high sensitivity troponin test.

*Adjusted for age, sex, and post-implementation of hsTn and statistically significant variables from stepwise variable selection: CAD, Diabetes, AFIB, HF, Troponin test results, CT scan, and consultation. Bold indicates a statistically significant result.

Chapter 4 Figures

Figure 4.1 Accelerated chest pain protocols before-and-after introduction of high sensitivity troponin.

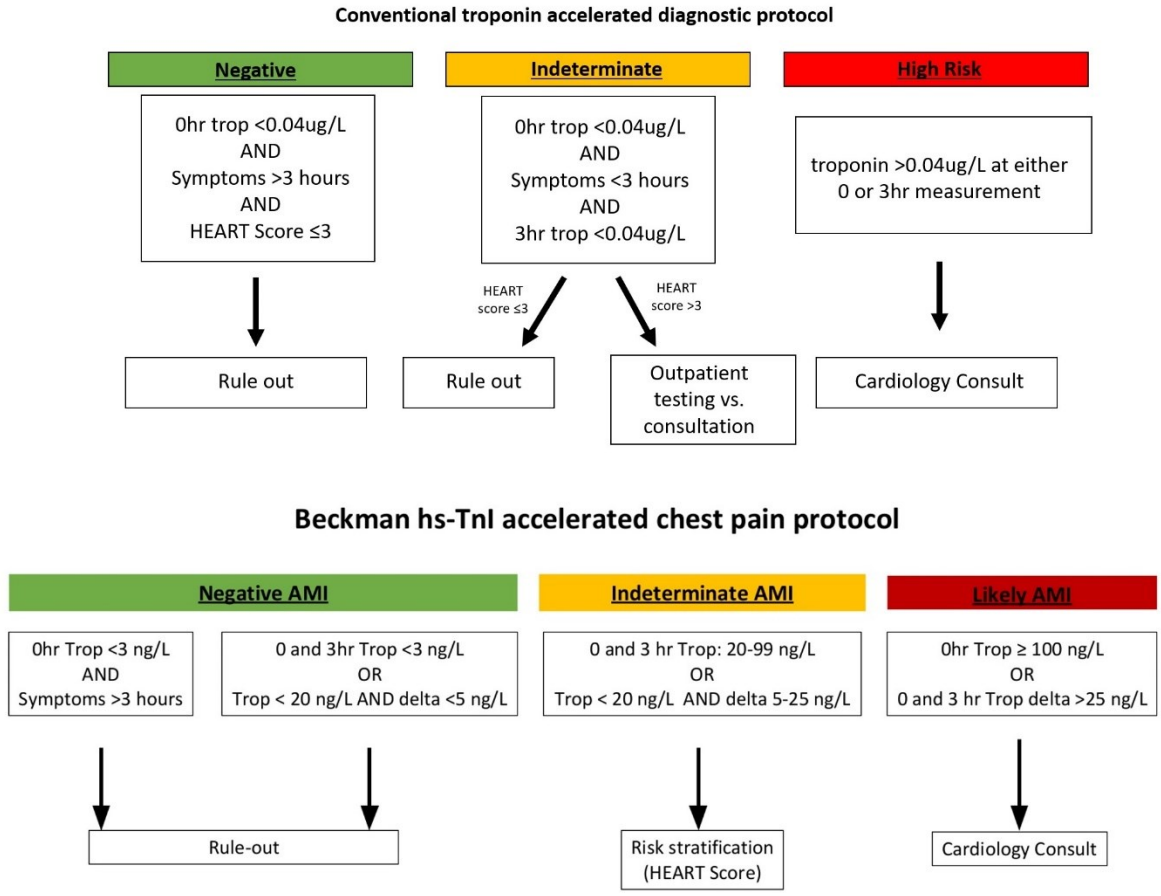


Figure 4.2 Trends in MACE within 30 days of index ED visit for patients with chest pain before and after the introduction of an accelerated pathway using a high-sensitivity cardiac troponin assay and a 3-hour serial troponin interval.

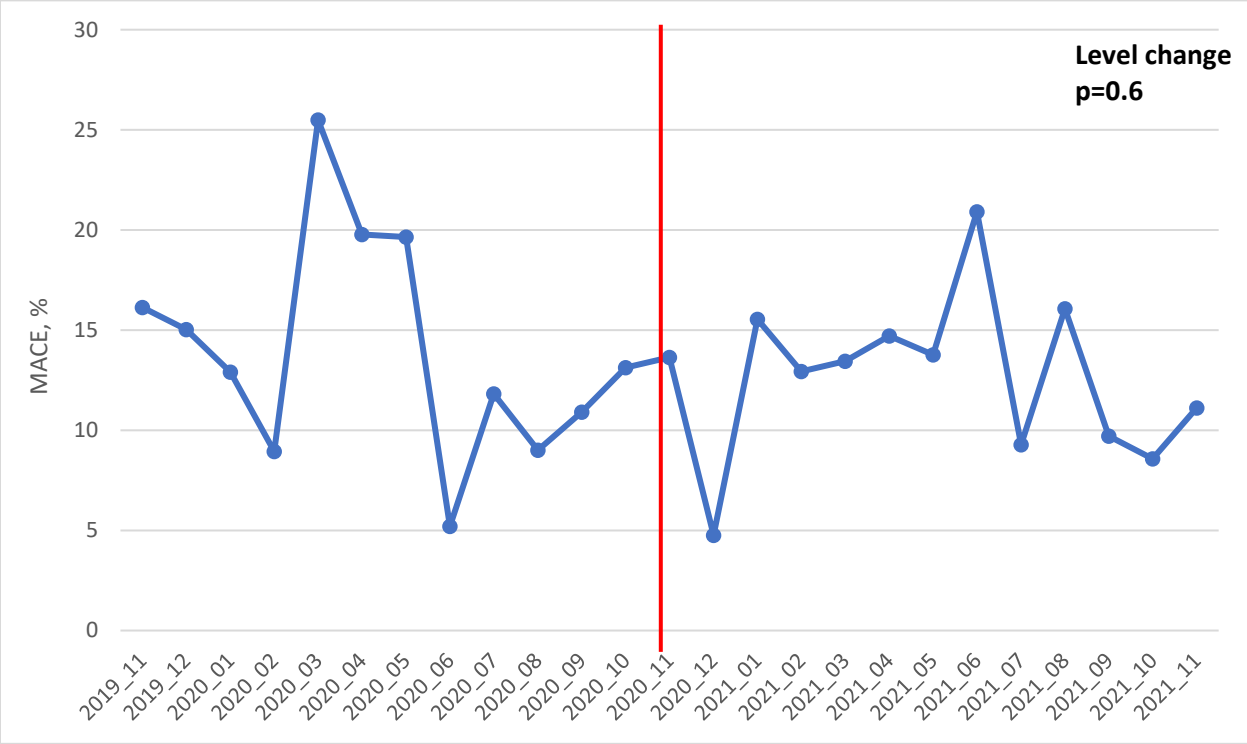
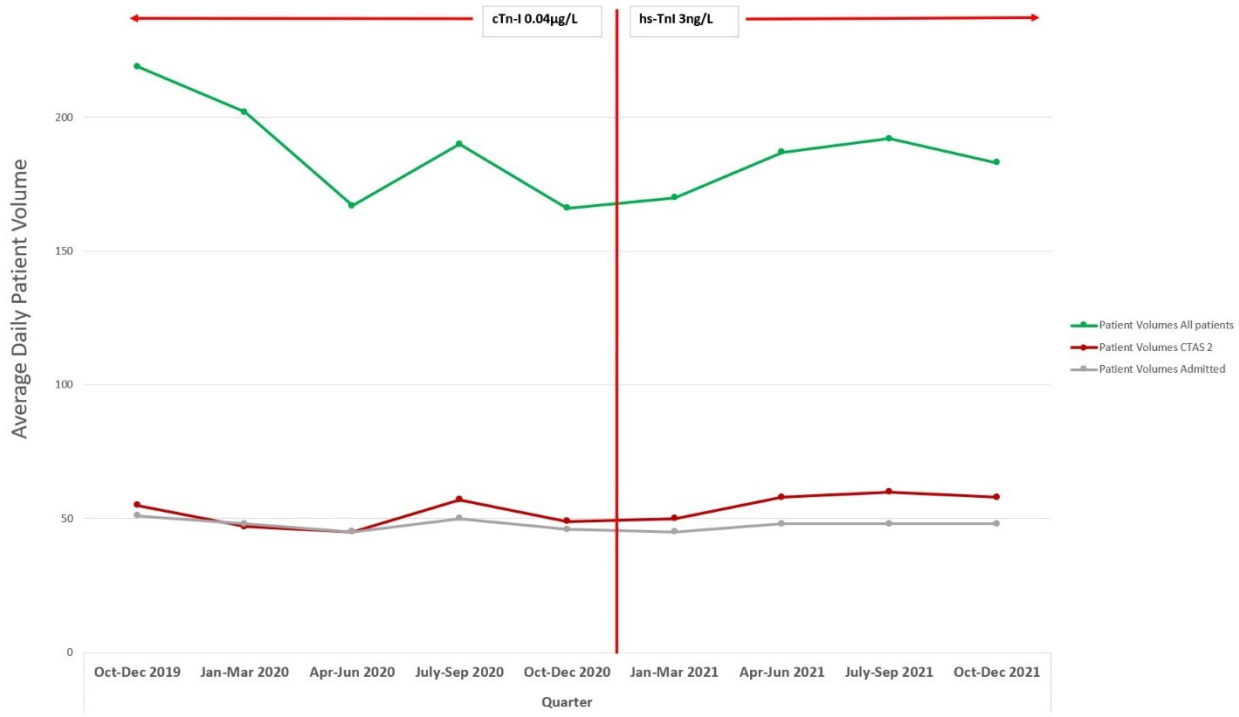


Figure 4.3 Patient volumes as a function of time throughout the study periods at the Royal Alexandra Hospital.



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Chapter 5: Conclusions and Future Directions

Importance

There are numerous reasons to expect emergency department overcrowding (EDOC) will continue to feature prominently amongst the most important issues facing our healthcare system here in Canada. Some of the most apparent reasons would include an aging population, rapid population growth, and a declining number of inpatient hospital beds (when adjusted for population). Presentations to the ED for chest pain are, and will continue to be, a major component of ED volume. Any efforts to improve care and minimize patients' length of stay within the ED are worth evaluating as one prong of a system-wide approach to reduce EDOC.

Implications of Findings – Chapter 2

The research described in this thesis supports the use of accelerated diagnostic protocols (ADPs), with or without the introduction of a high-sensitivity troponin (hs-Tn), to reduce ED length of stay (ED LOS) for adult patients with chest pain of suspected cardiac origin. This benefit was demonstrated in a systematic review involving 21 studies across multiple countries with vastly different healthcare systems and across disparate individual EDs with annual patient census ranging from 12,000 to 200,000. More detailed reporting on individual ED characteristics, including annual census, bed capacity, access to cardiology services, would help clinicians and administrators decide whether published data are applicable to their unique settings.

Another key finding from the systematic review was that not all patients presenting with chest pain achieve the same benefit of the interventions to reduce ED LOS. For example, patients with a significantly elevated initial Tn assay would not be expected to derive any benefit from a decrease in serial measurement timing. Separating these patients prior to analysis, when possible,

should be encouraged in future research reporting. It is possible that previously published modest reductions would be more impressive among the subset of patients who received serial troponin measurements. It is important that these review findings result in more standardized reporting in future studies.

Implications of Findings – Chapter 3

Like may other EDs in Canada, the RAH is adapting and adopting new protocols to better serve their patients, especially those with chest pain of cardiac origin. The first retrospective administrative database before-after study compared a 6-hour, c-TnI assay cut point of < 0.15 ug/L to a 3-hour, c-TnI assay cut-point of 0.04 ug/L, and a formalized ADP, over identical one-year periods. The enrollment samples appeared similar on multiple baseline characteristics, and the 3-hour, c-TnI cut-point of 0.04 ug/L demonstrated a significant decrease in median ED LOS (412 min vs. 378.5 min; p=0.035) for patients who were eventually discharged from hospital. Additionally, there was a decrease in re-admissions due to heart failure following ADP introduction (4.0% vs. 2.4%; p=0.010). These benefits came without an associated increase in the proportion of patients either requiring specialist consultation (36.1% vs. 33.8%; p=0.17) or experiencing Major Adverse Cardiac Events (MACE) (15.9% vs. 15.3%; p=0.62). Overall, the implementation of the 3-hour ADP with a conventional Tn assay was a safe and effective means to improve the efficiency of ED evaluation of patients presenting with chest pain of cardiac origin.

Implications of Findings – Chapter 4

The second retrospective administrative database before-after study compared a 3-hour, c-TnI assay cut point of < 0.04 ug/L (40 ng/L) to a 3-hour, hs-TnI assay with a detection threshold of 3 ng/L, over identical one-year periods. The enrollment samples appeared similar on multiple baseline characteristics, and the 3-hour, hs-TnI demonstrated a significant decrease in median ED LOS (392 min vs. 371 min; p=0.020) across all patients. The effect size was even more impressive when subgrouping only those patients who were eventually discharged from hospital (398 min vs. 363 min; p<0.0001), and those discharged after at least 2 troponins (477 min vs. 410 min; p<0.0001). Again, there was no statistically significant change in the proportion of patients admitted, requiring consultation, or experiencing MACE following the change to the hs-TnI assay. Overall, the implementation of the 3-hour ADP with a hs-TnI assay was successful, safe, and efficient.

Future Research

While these findings are reassuring there are many potential avenues for future research.

Demographic differences: Previous data has shown clearly that patients receive different care for similar ED chest pain presentations depending on several demographic factors, including age, sex/gender, and/or race[1,2]. While men have more cardiovascular disease[3], women are known to present more commonly with atypical chest pain than men[4]; however, even when presenting with classic cardiac pain and associated risk factors, women were found to receive fewer investigations than men[5]. Future research should explore sex-based differences in these patients.

Moreover, patients who self-identify as Black in the United States of America (USA) were less likely to have an electrocardiogram (ECG) or cardiac enzymes ordered[9]. It is unclear if

similar disparities in care are present for patients who self-identify as Indigenous (e.g., First Nations, Inuit, and Métis people) within the Canadian context. More research in the areas of Indigenous health and equity, diversity, and inclusion (EDI) are warranted; however, Indigenous and race-based identifiers will need to be collected on all patients for clarity to emerge.

Discrepancies in ED care for patients with chest pain begin even before any physician assessment. Triage scoring can significantly impact how long a patient may wait to be seen. Research evaluating triage nurse decision making demonstrated that patients aged 30 to 40 years were taken less seriously and felt to be "dramatic;" similarly, nurses reported being less likely to consider myocardial infarction as a diagnosis for female patients[1]. A large American data set from 1997-2006[2] revealed that Black patients presenting with chest pain were less likely to be triaged as emergent than White counterparts. In Canada, the Canadian Triage and Acuity Scale has added more modifiers to its chest pain scoring in recent years[6] to account for more varied presentations. Despite this, additional research in this setting seems warranted.

These improvements in triage scoring as well as the more widespread use of evidenced-based chest pain assessment tools by ED physicians may lead to more uniform investigations and outcomes. This assumption has yet to be proven and it will be important to demonstrate whether chest pain protocols have benefits beyond the reduction in ED LOS.

Protocol adherence: The impact of introducing a new protocol (Chapter 3 and 4) will depend in large part on the strategy employed to implement it. Practical considerations, including ease of use and understanding, factor greatly in terms of physician uptake. Even within rigorous randomized controlled trials, recent research[7] has shown that protocol adherence often falls well below 90%. In the context of retrospective data sets with much less coordinated oversight, it is reasonable to assume the adherence would be far lower than 90%.

It would likely prove valuable to evaluate what the overall protocol adherence was at our site throughout the various changes in chest pain protocols. Detailed information on which situations lead to higher proportions of protocol non-adherence may provide insight on how to better tailor future protocols to align with clinical practice. Additionally, if we can provide feedback in a general fashion to clinicians about how protocol non-adherence affects clinical and operational outcomes, they may be more likely to alter their practices.

New troponin assay: Due to a mandate from the provincial healthcare authority, the Royal Alexandra Hospital (RAH) ED underwent another change in its troponin assay on September 27, 2022. This represents a natural experiment and an ideal opportunity to repeat a similar evaluation exercise to assess whether the new protocol is efficient, effective, and safe. The new protocol revised serial testing to a 2-hour hs-Tn and employs a hs-TnT assay. Additionally, it introduces a much more complicated pathway with more branches than any of the previously studied protocols. This complexity will likely have implications on the adherence and potentially the effectiveness of the new pathway.

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