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Risk Scores for Predicting Mortality in Flail Chest

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A thesis submitted in partial fulfillment of the requirements for the degree in Master of Science

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RISK SCORES FOR PREDICTING MORTALITY IN FLAIL CHEST

(Thesis format: Integrated Article)

by

Meaghan ZEHR

Graduate Program in Epidemiology and Biostatistics

A thesis submitted in partial fulfillment
of the requirements for the degree of
Master of Science

The School of Graduate and Postdoctoral Studies
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London, Ontario, Canada

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Abstract

The objective of this thesis was to develop two risk scores which could predict the individual risk of in-hospital mortality for patients with flail chest using data from the Ontario Trauma Registry. The first study describes the univariate analyses conducted to identify mortality predictors. The second study details the logistic regression analysis that generated a risk score. Finally, the third study describes the decision tree analysis that produced the second risk score. The two risk scores were then compared.

In summary, these three studies show that a minority of flail chest patients are currently receiving operative repair and that a risk score may be a useful adjunct for surgeons to determine the individual risk of in-hospital mortality in patients requiring operative repair for flail chest.

Keywords

Flail chest, risk score, operative repair, mortality, prediction model, logistic regression, decision tree

Co-Authorship Statement

The three studies described here were designed and executed by Meaghan Zehr. This includes but is not limited to study conception, data analysis and interpretation. Regular feedback was provided by the supervisory committee. Each of the manuscripts was authored primarily by Meaghan Zehr.

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List of Abbreviations

Description	Abbreviation
Abbreviated Injury Scale	AIS
Acute Physiology And Chronic Health Evaluation scale	APACHE
Cardiopulmonary resuscitation	CPR
Charlson Comorbidity Index	CCI
Computed Tomography scan	CT scan
Glasgow Coma Scale	GCS
Injury Severity Score	ISS
Intensive Care Unit	ICU
Maximum Abbreviated Injury Scale	MAIS
National Trauma Data Bank	NTDB
National Trauma Registry	NTR
Ontario Trauma Registry	OTR
Receiver Operating Characteristic curve	ROC curve
Revised Trauma Score	RTS
Revised Trauma Score and Injury Severity Score	TRISS

Chapter 1

1 Introduction

Flail chest is a condition where two or more ribs are fractured in at least two places resulting in a section of the thoracic cage separating from the remainder of the chest wall (1). Occurring roughly in 20% of all rib fracture cases, it is frequently associated with long term pain, disability and mortality (1-4). Operative repair of the rib fractures may improve patient outcomes although many questions still need to be answered, including which patients would benefit the most from operative repair. The objective of this thesis is to create a risk score which can predict individual risk of in-hospital mortality to help surgeons identify which patients may benefit the most from operative repair.

This chapter will describe flail chest and introduce the role of operative repair as an adjunct to the current standard of care. The need for a risk score to identify individual risk of mortality in flail chest patients is explained. Afterwards, chapters two to four recount the analyses conducted to create the models. Chapter two describes the univariate analyses conducted to identify mortality predictors. Chapter three details the logistic regression analysis that generated a risk scoring system. Chapter four relates the decision tree analysis which produced a risk score. Finally, chapter five explains and interprets the study results and their implications to clinical practice and future research.

1.1 Description of flail chest

Flail chest patients typically present with severe pain, impaired respiratory function, and paradoxical motion of the chest wall with respiration (5). Diagnosis is confirmed by a chest radiograph or CT scan (5). Approximately one third of blunt trauma victims sustain rib fractures and most often from a motor vehicle collision although in an elderly, osteoporotic patient the force from a fall may be sufficient (1, 6). It is important to note that because of the sheer force of the injury, a flail chest is often associated with other life-threatening injuries (6). The mortality rate following flail chest is estimated to be between 10% and 36% of cases with most deaths occurring within the first 48 hours (3-

4). Flail chest is associated with several complications including severe pain, reduced lung volume and respiratory failure necessitating long term ventilation, ICU and hospital stays (5, 7). Mechanical ventilation, while potentially lifesaving, carries risks of pneumonia, septicemia, lung injury, lung collapse and tracheostomy (2, 8). Long term pain and disability are common after rib fractures (9). Landercasper et al. (10) found that five years after their injuries, only 43% of flail chest patients returned to work and 49% reported chest wall pain.

1.2 Epidemiology of flail chest

A recent 2014 epidemiology study used data from the National Trauma Data Bank of the United States and Canada and described 3,467 flail chest patients: the largest sample size of flail chest patients to date (11). Flail chest patients were on average 53 years of age and 77% were male (11). Moreover, approximately 80% of flail chest patients were admitted to intensive care (11). Injury characteristics included significant head injury in 15% of cases and lung contusion in 54% of cases (11). Nonoperative procedures included ventilation in 59% of cases, chest tubes in 44% of cases and tracheostomy in 21% of cases (11). In-hospital adverse events included pneumonia in 21% of cases, adult respiratory distress syndrome in 14% of cases, sepsis in 7% of cases, and death in 16% of cases (11).

1.3 Standard treatment of flail chest

The standard treatment of flail chest includes pulmonary toilet, pain control (i.e. oral analgesia, intercostal blocks, pleural infusion catheters, epidural analgesia) and ventilation when needed (6). Analgesia allows for adequate respiration however no significant differences in the length of stay in the intensive care unit or incidence of complications have been found between analgesic techniques (8). Prior to the 1975 seminal paper by Trinkle et al. (12), mechanical ventilation was used until the chest wall had fully healed, whether or not patients' respiratory function was compromised. Trinkle et al. (12) showed that by focusing efforts on the underlying pulmonary contusion and avoiding mechanical ventilation and tracheostomy, length of stay was reduced from

thirty-one to nine days ($p=0.005$) and complication rates were reduced from 100% to 20% ($p=0.005$). Now it is recognized that mechanical ventilation should only be used in cases of respiratory failure (3). Nonoperative treatment avoids potential surgical complications (i.e. infection, lung injury, future operations to remove implants) but requires constant pain control and in rare cases can result in malunion or nonunion which requires surgical correction (7).

1.4 Operative repair of flail chest

There is growing interest in operative repair as an adjunct to standard treatment: the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom issued a recommendation for operative repair of flail chest in 2010 (13). This organization has advocated operative repair in flail chest patients stating that although the quantity of evidence supporting operative repair is limited, it is consistent in efficacy and that no major safety concerns exist in the context of patients with severe trauma and impaired pulmonary function (13). However, there is still controversy regarding the benefits and risks of operative repair in flail chest (6). As a result, there is no absolute treatment protocol in North America: some surgeons support operative repair and others do not (7, 14). The basic methodology for surgical fixation is to stabilize the fracture after open reduction to normalize the shape of the chest wall to restore respiratory function (15). There are several techniques which can be used for rib fracture fixation: Kirschner wires, suture and traction, struts, Osteosynthesis implants, nails, and plates (7, 16). Figures 1-2 show examples of flail chest before and after operative fixation. It is unknown which, if any, fixation technique is best although Kirschner wires used alone are not recommended by NICE (7, 13). The best time to perform operative repair is also controversial: most authors have reported repairs two to five days after lead trauma hospital admission (17-19).

To date there have been three randomized controlled trials evaluating the efficacy of operative repair in flail chest which are summarized in Appendix A. The randomized controlled trials were unblinded and sample sizes ranged from 37 to 46 patients. Two of the three trials found that operatively repaired patients required significantly fewer days

on ventilation (seven to ten fewer days) and were 40% to 53% less likely to experience pneumonia (17-18). All trials reported that operatively repaired patients required significantly fewer days in intensive care (a difference ranging from five to ten days) (17-19). None of the trials found evidence of a significant difference in mortality between treatment groups suggesting that operative repair may not be a life-saving procedure (17-19).

Two recent meta-analyses, both conducted in 2013, including nine and eleven studies respectively (each including only two of the three RCTs: Tanaka and Granetzny) found that patients who underwent operative repair had significantly fewer days on mechanical ventilation (4.5 to 7.5 days, $p < 0.05$), significantly fewer days in intensive care (3.4 to 4.8 days, $p < 0.05$), significantly fewer days in hospital (3.8 to 4.0 days, $p < 0.05$), significantly reduced risk of mortality (RR 0.43, OR 0.31, $p < 0.05$), significantly reduced risk of pneumonia (RR 0.45, OR 0.18, $p < 0.05$) and significantly reduced need for tracheostomy (RR 0.25, OR 0.12, $p < 0.05$) (7, 16).

Operative repair has also been shown to be more cost-effective than standard of care by an average of \$1,541 per incremental quality of life unit (20). Furthermore, operative repair may reduce long term morbidity and pain almost to the level experienced by the general population (21). Six months after the injury, significantly more operatively repaired patients than non-operatively repaired patients were able to return to work (61.1% vs 5.3%, $p < 0.05$) (17). Additionally, operatively repaired patients had lower reports of persistent pain six months after injury than non-operatively repaired patients reported five years after injury (35% vs 49% for operatively repaired and non-operatively repaired patients respectively) (10, 22).

Nevertheless, surgical complications can occur including infection, lung injury and need for future operations to remove implants (7). Complication rates following surgery have not been well documented; however, Granetzny et al. found no evidence of a significant difference between treatment groups when comparing the number of complication-free patients and chest infection (18).

1.4.1 Unclear indications for operative repair

Operative repair is considered an effective procedure that is currently underused (4, 23). In their retrospective review, Cannon et al. (5) found that of the 164 patients admitted to their facility over a ten year period, only 1.3% underwent operative repair. A 2009 survey of American trauma, orthopaedic and thoracic surgeons conducted by Mayberry et al (14) identified lack of experience with the surgical techniques and need for refining operative indications as barriers to performing operative repair. Potential indications of operative repair include failure to wean from ventilation, paradoxical movement of the chest wall during ventilation, persistent pain, progressive decline in pulmonary function, no severe pulmonary contusion, and no significant brain injury (24, 25). Other candidates include patients with chest deformities too severe to heal on their own or patients who require thoracotomy for concomitant injuries (24). Also, cases of shock, multiple injuries, severe head injury, history of lung disease, ≥ 8 rib fractures, and over 65 years of age are less likely to undergo operative repair (2). The cause of respiratory dysfunction, supporting muscle strength, and cardiopulmonary condition may also need to be considered when determining who should undergo operative repair (26). Cases of flail chest involving more than four ribs where the two points of fracture are separated by at least 25% of rib length often require longer time on ventilation and may benefit from operative repair the most (26). The randomized controlled trials used various operative indications including need for mechanical ventilation, number and location of rib fractures (≥ 6 , lower ribs only); excluding severe head injury (head AIS >3 , “disturbed conscious level”, GCS <10), age (<14 years, >80 years), comorbidity, spinal injury and sepsis (17-19).

There are clearly numerous considerations when answering who benefits from operative repair. These indications are also somewhat dependent upon clinical judgment: how many days requiring ventilation is “failure to wean”, what is considered “severe” pulmonary contusion, what is “significant” brain injury. Researchers have attempted to identify markers of injury severity and risk factors for mortality to help guide clinical decision making. These studies are summarized in Appendixes B-F. The studies show that mortality may be related to number of rib fractures, age, multiple injuries, comorbidities, lung contusion, ventilation, shock, trauma scoring system scores, blood

transfusion and PaO₂/FIO₂ ratio (27-37). While these studies provide insight into which factors may influence mortality risk, the findings can conflict, the cut points vary, some information is not available before surgery (i.e. trauma scoring systems), some terms are too broadly defined (i.e. shock), and the clinical applications are unclear.

1.5 Trauma scoring systems

Trauma scores are designed to help physicians make diagnostic and therapeutic decisions at the bedside (38). They are developed from mathematical models that quantify injury severity and predict mortality in individuals (39). Stiell, the primary author of the Ottawa Ankle Rules, has suggested there are six stages in the formation of a mature clinical risk scoring system: justification for the risk score, calculation of the model, prospective validation of the model and refining it as necessary, implementation of the risk score into clinical practice, determination of cost-effectiveness of the risk score, and the widespread dissemination and implementation of the risk score (38). According to this paradigm, the models calculated in our thesis are in stage two of development and will need to be validated prospectively before they can be implemented into clinical practice. A risk score is more likely to be useful if the clinical condition is common, if there is significant variability in current practice among similar physicians or institutions, and if physicians strongly support the development of a risk score (38). In the case of flail chest, although it may be considered a rare condition, there is widespread variability in current surgical practice and surgeons have indicated that refinement of surgical indications is needed (5, 14).

1.5.1 Advantages and disadvantages

Risk scores have several advantages over human decision making: theoretically there is no upper limit to the number of factors they can account for, they always provide the same result to a given problem (although this may not be the correct result), and several studies have shown they may be more accurate than clinical judgment alone in some cases (40). However, with the increasing volume of risk scores it can be difficult to identify the “best” tool to use and the tool itself may not be very user-friendly (40).

Therefore when coming to a decision, physicians should recall the principles of evidence-based medicine: to integrate research evidence, clinical expertise, patients' values and preferences, and clinical circumstances (41). The intent of a risk score is to inform physicians and support them in coming to an appropriate solution for the patient.

1.5.2 Examples of trauma scoring systems

Physiological trauma severity scoring systems include the Glasgow Coma Scale (GCS), the Revised Trauma Score (RTS) and the Acute Physiology And Chronic Health Evaluation scale (APACHE) (42). Anatomical scoring systems include the Abbreviated Injury Scale (AIS) and the Injury Severity Score (ISS) (42). There are also combined anatomical/physiological systems such as the Revised Trauma Score and Injury Severity Score (TRISS) (42).

1.5.2.1 Glasgow Coma Scale

The GCS was developed to provide a standardized assessment of patient consciousness (43). It has motor, verbal and eye-opening behavioral response components (43). The scale ranges from three to fifteen where higher scores indicate improved consciousness (43). The GCS is simple to apply and can be assessed at the scene of injury, at the primary hospital or at the lead trauma hospital and as such it is available before operative repair but has limited ability to predict mortality on its own (42).

1.5.2.2 Other trauma scoring systems

The RTS and APACHE are very sensitive and are strong predictors of mortality but are difficult to calculate and are not available before operative repair (42). The AIS assigns a weighting to each patient injury and the maximum AIS (MAIS) of a body region is an excellent marker of injury severity but it is cumbersome to apply since each injury must be looked up in a dictionary manual which makes it unavailable before operative repair (42). The ISS is a strong predictor of mortality but it requires each injury be coded by the AIS system and as such is not available before operative repair (42). The TRISS is likewise an excellent predictor of mortality but makes use of the ISS and RTS and therefore is unavailable before operative repair (42).

1.5.3 Methods used to develop risk scores

The nature of the outcome of interest determines which modeling techniques may be employed. For a binary outcome such as mortality, there are several modeling techniques available including but not limited to logistic regression, artificial neural networks and decision trees (44). There are also hybrid approaches that make use of multiple techniques to generate a single model (45). We used logistic regression and decision tree prediction models.

1.5.4 Logistic regression

Logistic regression estimates the natural logarithm of the odds of a binary outcome given the linear combination of predictors (46). Certain considerations for logistic regression include the additivity and linearity assumptions (46). One form of the additivity assumption refers to situations where the effect of a predictor is independent of the effect of other predictors and can be assessed by the inclusion of interaction terms in the model (often between two variables although higher-order interactions are possible) (46). The linearity assumption refers to the log odds of the outcome being linearly related to continuous predictors and can be assessed graphically, using dummy variables, or by adding polynomial terms to the model (46). One example of a mortality risk prediction model which used logistic regression is the Berg et al. study which evaluated adult patients undergoing open-heart surgery at their institution over a seven year period (47). The study followed the modelling strategy outlined by Harrell et al. which is essentially a 15-step guide where the entire sample is used to train the model, the full model is used (or a pre-specified subset is tested) and the model is validated using bootstrapping (48). Bootstrapping is simply an internal validation method whereby a model is tested repeatedly on many subsets drawn with replacement from the original sample (48). This strategy is preferred over cross-validation techniques since it allows the analyst to make use of the entire sample to train the model (48).

1.5.5 Decision trees

A decision tree uses an approach called “recursive partitioning” to divide data into similar risk groups (49). When a split occurs two groups are formed where a case with the input value less than the split would fall into one group and a case with an input value greater than the split would fall into the other group (50). The two groups and the binary outcome (i.e. mortality) form a 2x2 contingency table and a test (such as the logworth) measures the difference in outcome proportion between the two groups (50). The bigger the difference in outcome proportion, the better the split (50). A test is performed for each possible split point so Bonferroni corrections can be applied to account for any accidentally large logworth which can occur with multiple testing (50). If there are subjects that are missing values for the splitting variable, then these subjects are added to the risk group that creates the best split (46). The splitting process is performed for each of the inputs and the biggest logworth is taken as the first split (50). Predictors may be used multiple times in a decision tree. Recursive partitioning continues until a pre-set stopping criterion ends the splitting process which may include all the end groups are of only one outcome type, the minimum number of observations is reached, or a threshold of impurity is met (50). Decision trees have several advantages including ease of interpretation, ability to be trained on small data samples, direct derivation of risk scores, robustness to irrelevant information (i.e. predictors that do not improve model performance will not be used to create risk groups), and usage of all data (including missing values) (44).

1.5.6 Artificial neural networks

Artificial neural networks consist of many interconnected processing elements each of which assigns weights to inputs where inputs are defined as the number of other connecting neurons and the weights represent the strength of the inter-neuronal connections (44). Each neuron has a threshold which will produce an output if the threshold is exceeded by the sum of the products of the inputs and weights (44). The goal is to classify an object into one of two classes based on feedback from of the error difference from the predicted and actual outputs (44). The advantages of neural networks

include their ability to detect complex non-linear relations between the outcome and predictors as well as all possible interactions between predictors (42). Disadvantages of neural networks include limited ability to detect causal relationships, difficulty in applying at bedside, and tendency to overfit the data (42). We chose not to perform neural network analysis due to time constraints and because this type of model may be overly optimistic (42).

1.6 Database registries in thoracic trauma

A trauma registry is a comprehensive data repository usually run by a hospital containing information about patient injury, demographics, pre-hospital care, in-hospital treatment and outcomes (51). Regional trauma registries contain information for multiple hospitals in a state or province and are frequently used for policy making (51). However, trauma registry data usually contains some missing information; especially physiological variables such as the GCS (52).

In Canada there is a provincial trauma registry for Ontario known as the Ontario Trauma Registry (OTR) and a federal trauma registry called the National Trauma Registry (NTR). The epidemiology of flail chest study described earlier made use of the National Trauma Data Bank (NTDB) which is the federal trauma registry of the United States.

1.6.1 Ontario Trauma Registry

The OTR was established in May 1992 by the Ontario Ministry of Health and Long-Term Care (53). The OTR is composed of three data sets: the Comprehensive Data Set, the subset of the NTR, and the Death Data Set (53). Our project made use of the Comprehensive Data Set of the OTR. This data set includes major trauma hospitalizations in the 11 lead trauma hospitals in Ontario (for the complete list of lead trauma hospitals in Ontario please refer to Appendix G) (53). To be included in this data set patients must have had an ISS greater than 12 and have been admitted to a lead trauma hospital or have been treated in the emergency department of a lead trauma hospital or have died in the emergency department of a lead trauma hospital after

receiving treatment (53). In 2009 to 2010 there were 4,235 injury cases and 455 in-hospital deaths which represents 10.7% mortality for all included trauma cases in Ontario (53).

1.6.2 National Trauma Registry

The NTR was established in 1997 and is composed of two data sets: the Minimum Data Set and the Comprehensive Data Set (54). It closed on March 31, 2014 partly due to its limited use by jurisdictions (54). The Comprehensive Data Set includes patients hospitalized for major trauma in British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, New Brunswick, Nova Scotia and Newfoundland and Labrador (54). The sources of this data set are the 108 facilities equipped for major trauma across nine provinces (in some provinces these facilities are designated lead trauma hospitals and in other provinces trauma care is integrated into primary hospitals) (54). To be included in this data set, patients must have had an ISS greater than 12, have had an external cause of injury consistent with trauma, and have been admitted to a lead trauma hospital or have been treated in the emergency department of a lead trauma hospital or have died in the emergency department of a lead trauma hospital after receiving treatment (54).

1.6.3 National Trauma Data Bank

The NTDB was established in 1989 and includes 805 trauma facilities in the United States (55, 56). Also, it has recently expanded to include St. Michael's Hospital in Toronto, Ontario. It contains over five million patient records (55). Its mandate is to inform medical practitioners, the public, and decision-makers about the current state of care for injuries (55).

1.7 Research rationale

There is a need to identify which flail chest patients would benefit the most from operative repair (14). A risk score including preoperative covariates could be used to determine individual risk of mortality thus identifying potentially unfavorable surgical candidates. Since there is no one optimal modeling strategy, logistic regression and

decision tree methodologies were both selected. The models were trained on ten years of data from the Ontario Trauma Registry to form risk scores. These methodologies are appropriate for a binary outcome such as in-hospital mortality and each has a different approach of estimating risk. Logistic regression can quantify the strength of predictors through odds ratios while decision trees assign importance based on the variable placement in the tree hierarchy (48). Both decision trees and logistic regression (using the Harrell et al. strategy) can be trained on small data sets (42, 46). The Ontario Trauma Registry is well-established and contains comprehensive data on all lead trauma hospitalizations for flail chest (52). The results of these analyses will provide two risk scores each calculating individual risk of mortality. The model performances can then be compared to identify which approach best captured mortality risk.

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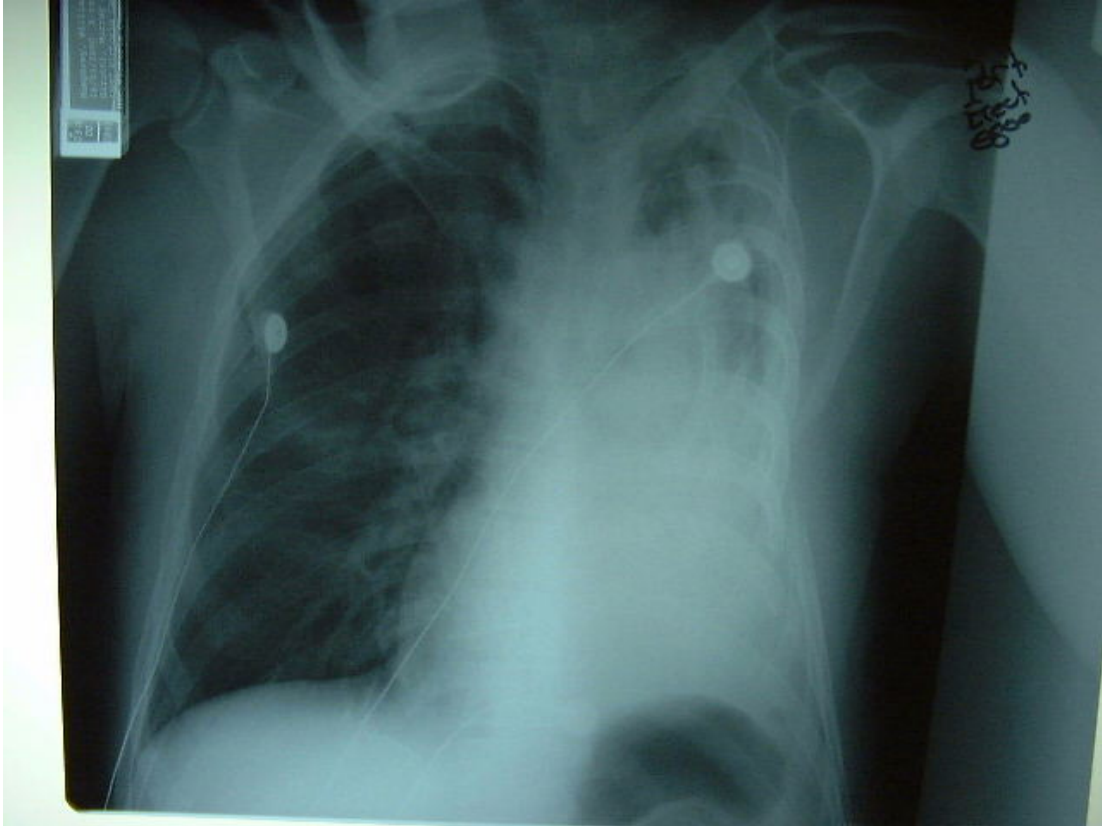


Figure 1: Unfixed flail chest on left side with collapsed lung

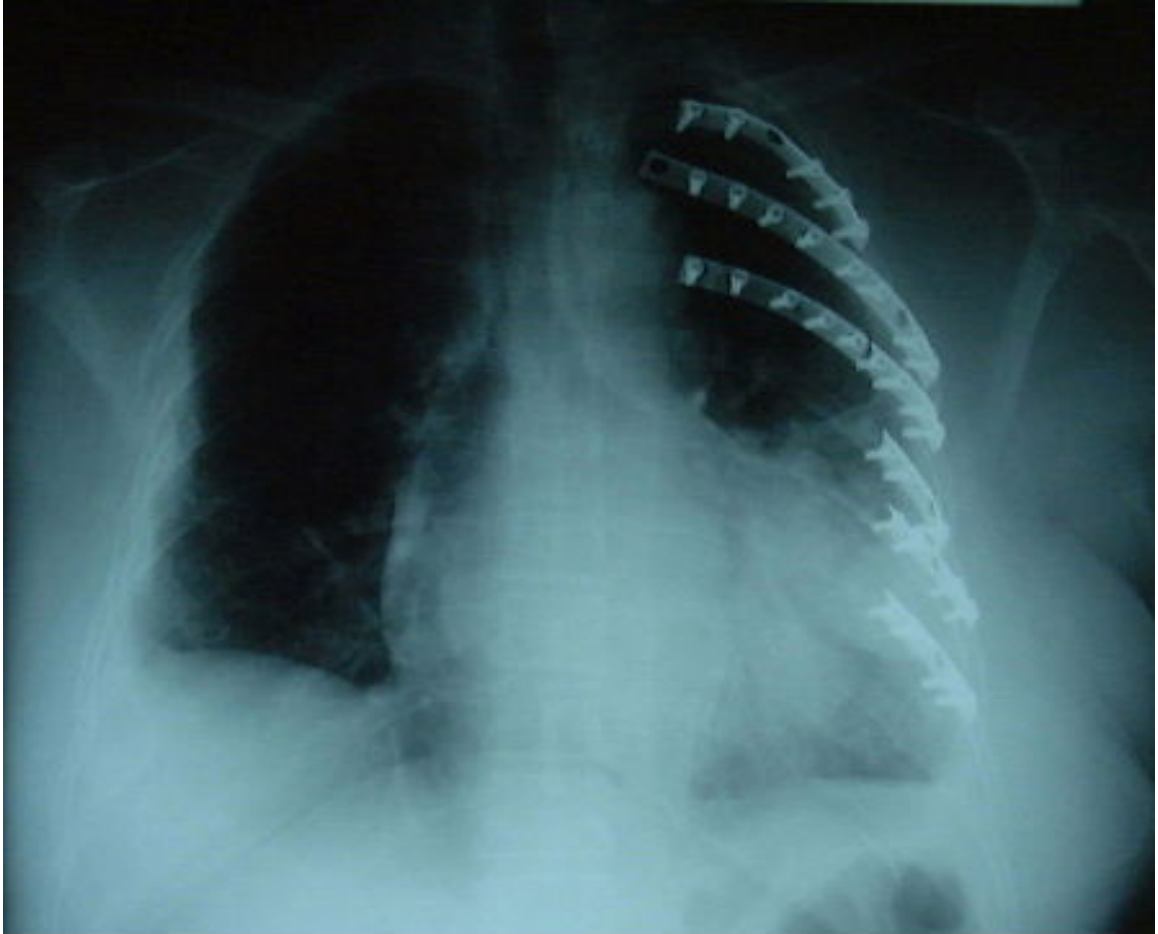


Figure 2: Operative repair of flail chest using plates and screws

Chapter 2

2 Operative repair of flail chest in Ontario, Canada: Who's getting picked?

2.1 Introduction

Flail chest is a severe type of rib fracture with an estimated mortality rate of 10% to 36% (1-4). Several studies including two meta-analyses and three randomized controlled trials have shown that operative repair, when compared to standard of care practice, restores normal ventilation earlier among cases of respiratory failure; decreases overall length of stay in the intensive care unit and hospital; reduces the total cost of care; and reduces the rates of ventilator-associated pneumonia, tracheostomy, sepsis, barotrauma and mortality (5-10). Despite these benefits to patients, operative repair remains an underused procedure (11, 12).

One reason for the paucity of operative repairs is the uncertainty of what characterizes a suitable flail chest for operative repair (13). Potential indications include failure to wean from ventilation, paradoxical movement of the chest wall during ventilation, persistent pain, progressive decline in pulmonary function, no severe pulmonary contusion, and no significant brain injury (14-15). Although more severe cases are easily assessed, less severe patients may be more difficult to classify.

Researchers have attempted to identify markers of injury severity and risk factors for mortality to help guide clinical decision making. Several studies show that mortality may be related to number of rib fractures, age, multiple injuries, comorbidities, lung contusion, ventilation, shock, trauma scoring system scores, blood transfusion and PaO₂/FIO₂ ratio (16-22). While these studies identify factors that may influence mortality risk, the findings can conflict, the cut points vary, some information is not available before surgery (i.e. trauma scoring systems), some terms are too broadly defined (i.e. shock), and the clinical applications are unclear.

The study objective was to identify characteristics of flail chest patients selected for operative repair in Ontario, Canada and if these indicate improved survival.

2.1 Methods

2.1.1 Data collection and processing

All adult flail chest patients who survived at least 24 hours after hospital admission were identified in the Comprehensive Data Set of the Ontario Trauma Registry (OTR) from January 1, 1999, to March 31, 2009. The OTR was established in 1992 and its direct sources are the 11 lead trauma facilities in Ontario. They are mandated to report demographic, pre-hospital and hospital care, and patient outcomes on all adult hospitalizations due to major trauma (23). Two lead trauma facilities which are children's hospitals (Hospital for Sick Children, Children's Hospital of Eastern Ontario) did not treat any adult flail chest cases. The nine remaining facilities are listed in Table 2-1. Cases of flail chest that may not be captured by the OTR would include isolated single system injuries and untreated cases of mortality (dead on arrival or dead at the scene). The data quality of the OTR is maintained by the Canadian Institute for Health Information (23). The OTR has patient-level information on demographics, up to 27 injuries, procedures and outcomes (23).

Twenty-three patient characteristics were analyzed including age, sex, number of comorbidities, number of fractured ribs, Injury Severity Score, Glasgow Coma Score, Maximum Abbreviated Injury Score in the head/neck region, first recorded heart rate at lead trauma hospital (bpm), first recorded unassisted respiratory rate per minute at lead trauma hospital, first recorded systolic blood pressure at lead trauma hospital (mm Hg), first recorded blood alcohol concentration at lead trauma hospital (mmol/L), non-operative procedures performed at primary or lead trauma hospitals, total length of stay in special care units and in lead trauma hospital and discharge status from lead trauma hospital as dead or alive. The Ontario Trauma Registry defines special care units as intensive care units with at least one nurse for every two patients (23). Comorbidities

were identified using the Quan et al. (2005) coding algorithms for Charlson and Elixhauser comorbidities (24). Lead trauma hospitals were de-identified.

2.1.2 Statistical analyses

All analysis was conducted using SAS software, version 9.4 (SAS Institute, Inc, Cary, NC). All tests were two-sided and the Bonferroni correction was applied to account for multiple testing (i.e. p-value of 0.05 divided by 23 variable comparisons results in significance level of $p < 0.002$). Skewness was assessed somewhat subjectively for each group using Q-Q plots. If skewness was graphically indicated, medians and distribution-free confidence intervals were reported instead (25). P-values for skewed variables were calculated using the Wilcoxon rank sum test. Continuous normally-distributed variables were analyzed using an independent t test assuming unequal variances. Categorical and binary variables were analyzed using the Fisher's exact test.

2.2 Results

Figure 3 shows the breakdown of flail chest patient outcomes. There were 34,006 adult trauma cases in the Ontario Trauma Registry from January 1, 1999, to March 31, 2009 of which 1,190 (3.5%) were flail chests. One hundred and eight flail chest patients (9.1%) died within the first twenty-four hours in hospital and an additional 97 flail chest patients (8.2%) died afterwards. There were 42 operative repairs performed. Eight of the nine lead trauma hospitals in Ontario performed at least one operative repair of flail chest.

Table 2-2 compares operatively and non-operatively repaired flail chest patients who survived at least 24 hours in hospital. There was no evidence of any statistically significant differences between patients who underwent operative repair and those who did not with regards to age, sex, blood pressure, heart rate, respiratory rate, blood alcohol content, ISS, GCS, MAIS, number of fractured ribs, comorbidities, blood transfusion, definitive airways, ventilation, chest tubes, thoracotomies, and CPR. Interestingly, of those patients who underwent operative repair, there seems to be fewer treated in later years ($p < 0.0001$). It is not readily apparent why this occurred. Also, patients who underwent operative repair stayed in the special care

unit 7.5 more days on average than patients who did not undergo operative repair ($p=0.0005$). Operatively repaired patients tended to stay in the hospital for eight days longer than non-operatively repaired patients although this did not reach statistical significance after correcting for multiple testing ($p>0.002$). There was no evidence of a statistically significant difference in mortality between operatively and non-operatively repaired patients ($p=0.17$).

Table 2-3 summarizes the characteristics of flail chest patients who survived at least 24 hours in hospital by discharge status. On average survivors were over ten years younger than mortality cases ($p<0.0001$), had less severe injuries ($p<0.0001$), had a higher Glasgow Coma Scale (GCS) score ($p<0.0001$), had a lower Maximum Abbreviated Injury Severity (MAIS) in head/neck region score ($p<0.0001$), had fewer or no comorbidities ($p<0.001$), did not require a definitive airway ($p<0.0001$), tended not to have respiratory failure and therefore did not require mechanical ventilation ($p<0.0001$), and tended not to require cardiopulmonary resuscitation ($p<0.001$). The survivors spent significantly more time in hospital, an average of eight more days, and had a shorter stay in special care unit although this did not reach statistical significance ($p<0.001$ and $p<0.0051$ respectively).

Table 2-3 suggests possible predictors of survivorship include a mean age in low fifties, ISS in low thirties, GCS of 15, MAIS in head/neck region of 3, did not receive CPR, without a definitive airway, without ventilation and without comorbidity. Table 2-2 shows that both operatively repaired patients and non-operatively repaired patients were on average approximately 50 years of age, ISS of 32 to 36, GCS of 15, MAIS in head/neck region of 3, did not receive CPR and without comorbidity. Operatively repaired patients had a higher percentage of definitive airway and ventilation use than survivors.

2.3 Discussion

Our study was the second largest study of flail chest patients to date. It examined 23 characteristics of 1,082 flail chest patients who survived at least 24 hours in hospital. It contrasted characteristics of patients who did or did not undergo

operative repair then described differences in patients who survived or died in hospital. We found no evidence of any significant difference between operatively repaired patients and non-operatively repaired patients with regards to demographics, injuries, procedures and mortality. Our results showed that there have been fewer operative repairs performed in recent years ($p < 0.0001$). Possible explanations for this could be budget costs in hospital where operative repair is perceived as more expensive than standard of care (despite the evidence of a recent cost-effectiveness study suggesting the opposite is true), lack of surgical training, lack of awareness of randomized controlled trials, limited operating room time resources, or that current surgeons prefer not to operatively repair their patients (10). The reasons are not clear. Additionally, our study found that patients who underwent operative repair stayed in the special care unit 7.5 more days on average than patients who did not undergo operative repair ($p = 0.0005$) which contrasts sharply with what was reported by two meta-analyses and three randomized controlled trials (5-9). This may be because Canadian surgeons consider the time duration for failure to wean off ventilation as approximately one week or that the operative repair procedure itself results in longer recovery times.

There were several similarities between flail chest patients recorded in the Ontario Trauma Registry and those recorded in the National Trauma Data Bank including age, sex and number of chest tube procedures (26). Some differences included lower rates of ventilation in Ontario (33% vs 59%), lower rates of tracheotomies in Ontario (<1% vs 21%) and lower rates of mortality in Ontario (9% vs 16%) (21).

Our results identified several potential mortality risk factors including age, ISS, GCS, MAIS, number of comorbidities, definitive airway, ventilation, and CPR. Similar to what has already been reported by the literature, we found that age, Injury Severity Score, Glasgow Coma Scale, number of comorbidities and ventilation appeared to be risk factors for mortality in flail chest patients (16-19). We found no evidence that number of rib fractures or blood transfusion were significantly associated with mortality but that CPR and definitive airway could be such (1, 16-22). The finding that there was no evidence to support that the number of rib

fractures influences risk of mortality is particularly significant since several studies have documented this effect (16, 18-22). This was most likely observed because over 80% of flail chest patients have at least five broken ribs and so there was not enough variation in this cohort to observe a difference in mortality risk.

One limitation of our study was that only 42 of 1,082 flail chest patients who survived at least 24 hours after hospital admission underwent operative repair which limited our statistical power to detect differences between operative and non-operative repair groups. However, this limitation reflects the fact that few surgeons currently perform them (11, 12). In fact, we observed that one institution did not perform any operative repairs of flail chest at all. Our study analysis was further limited by which parameters were available in the OTR. There are other important survival factors such as pulmonary contusion or shock which we chose not to analyze because the extent of these was not adequately captured in the database. Furthermore, our study only considered survival as an outcome and there may be other outcomes of interest to surgeons when evaluating flail chest patients for operative repair such as quality of life. However, all-cause mortality is a hard outcome and is perhaps the most patient-important outcome for consideration.

The strength of our study was that it included a large number of flail chest patients which was important so that an accurate classification of what characteristics were selected for operative repair in Ontario, Canada could be made. Furthermore, to our knowledge this was the first study to examine the characteristics of flail chest patients selected for operative repair and if these characteristics are associated with improved survival. The results of our analysis could be used as part of a risk score to assist surgeons considering operative repair for their flail chest patients.

2.4 Conclusions

Our study found that operative repair is performed in only a minority of patients that could benefit from it and that it did not appear to influence risk of mortality. Our study's results found that mortality risk factors for flail chest include age, Injury Severity Score, Glasgow Coma Scale, number of comorbidities, ventilation, CPR

and definitive airway. Additionally, it is unclear how flail chest patients are selected for operative repair since there does not appear to be any difference between treatment groups with respect to the mortality risk factors observed in our study. Further research should identify how strongly these risk factors are associated with mortality. Using these predictors in a risk score has the potential to quantify the individual risk of mortality and may be a useful tool in identifying a greater pool of patients eligible for operative repair.

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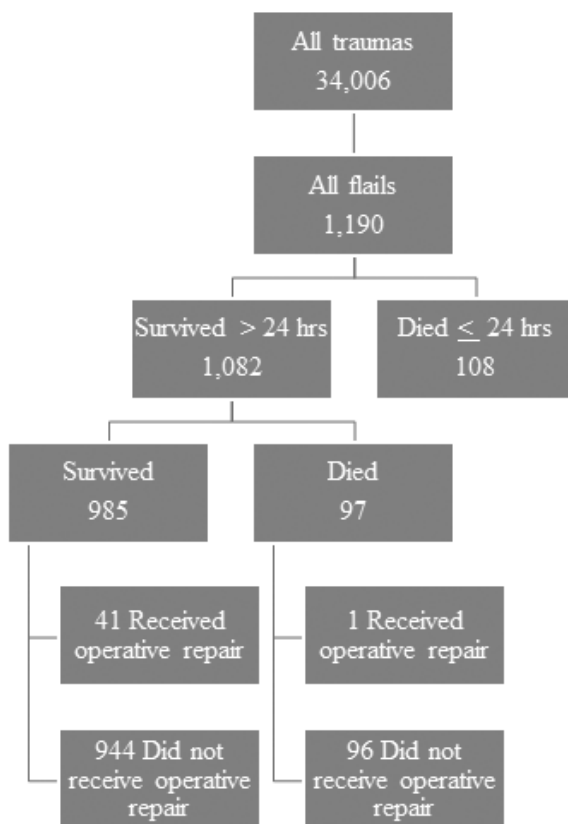


Figure 3: Patient outcome flow chart

Table 2-1: List of the 9 lead trauma hospitals and geographical location in Ontario

Facility	City
Hamilton Health Sciences Corporation	Hamilton
Hotel Dieu-Grace Hospital	Windsor
Kingston General Hospital	Kingston
London Health Sciences Centre	London
St. Michael's Hospital	Toronto
Sudbury Regional Hospital	Sudbury
Sunnybrook Health Sciences Centre	Toronto
The Ottawa Hospital	Ottawa
Thunder Bay Regional Hospital	Thunder Bay

Table 2-2: Characteristics of OTR flail chest patients who survived >24 hours by operative repair group

Characteristic (n)	Non-operative group (n=1,040)	Operative group (n=42)	p-value
Age (years) (n=1,082)	52.5 (51.4-53.5)	49.5 (44.2-54.8)	0.28
Sex (female) (n=1,082)	28.3% (25.6%-31.0%)	28.6% (15.7%-44.6%)	1.00
Proportion in 2004-2009 (n=1,082)	63.9% (61.0%-66.9%)	9.5% (2.7%-22.6%)	<0.0001
Systolic blood pressure (mm Hg) (n=1,055)	132.2 (130.4 -134.0)	133.0 (122.2 -143.9)	0.88
Hypertension (n=1,055)	41.6% (38.6%-44.7%)	41.5% (26.3%-56.5%)	1.00
Hypotension (n=1,055)	7.7% (6.1%-9.3%)	9.8% (2.7%-23.1%)	0.55
Heart rate (bpm) (n=1,058)	97.2 (95.8-98.5)	98.0 (90.9-105.2)	0.81
Respiratory rate (n=699)	22.1 (21.6-22.7)	24.2 (21.2-27.1)	0.18
Positive BAC ^a (n=823)	16.9% (14.3%-19.5%)	27.8% (14.2%-45.2%)	0.11
Injury Severity Score (n=1,082)	32.0 (31.3-32.7)	35.9 (31.7-40.1)	0.07
Glasgow Coma Scale (n=950)	15 (15-15)	15 (15-15)	0.51
MAIS ^b (n=615)	3 (3-3)	3 (2-4)	0.85
Fractured ribs (n=633)			
1	1.3% (0.6%-2.5%)	6.3% (0.2%-30.2%)	0.10

2-4	15.6% (12.8%-18.7%)	25.0% (7.3%-52.4%)	
5+	83.1% (80.0%-86.0%)	68.8% (41.3%-89.0%)	
Comorbidities ^c (n=1,082)			
0	81.9% (79.5%-84.2%)	83.3% (68.6%-93.0%)	0.86
1-2	16.1% (13.9%-18.4%)	14.3% (5.4%-28.5%)	
≥3	2.0% (1.3%-3.1%)	2.4% (0.1%-12.6%)	
Transfusion (n=1,082)	11.0% (9.1%-13.0%)	2.4% (0.1%-12.6%)	0.12
Definitive airway ^d (n=1,082)	40.7% (37.7%-43.7%)	54.8% (38.7%-70.2%)	0.08
Ventilation (n=1,082)	33.1% (30.2%-36.0%)	45.2% (29.9%-61.3%)	0.13
Chest tubes (n=1,082)	45.8% (42.7%-48.9%)	57.1% (41.0%-72.3%)	0.16
Thoracotomy (n=1,082)	0.7% (0.3%-1.4%)	0.0% (0.0%-0.0%)	1.00
CPR performed (n=1,082)	1.0% (0.5%-1.8%)	0.0% (0.0%-0.0%)	1.00
Days in special care units (n=1,082)	6 (5-6)	13.5 (7-19)	0.0005
Days in lead trauma hospital (n=1,073)	14 (13-16)	22 (12-38)	0.0125
Proportion survived (n=1,082)	90.8% (88.8%-92.5%)	97.6% (87.4%-99.9%)	0.17

^a Patient exceeded maximum legal blood alcohol limit for drivers in Ontario (i.e. 17.4 mmol/L or 0.08%).

^b Maximum Abbreviated Injury Score for the head and neck region.

^c Charlson and Elixhauser comorbidities were extracted from the ICD-9-CM and ICD-10 administrative codes using the Quan et al. (2005) coding algorithms. Comorbidities accounted for by both Charlson and Elixhauser methods were only counted once.

^d Definitive airway includes oral intubation, nasal intubation or tracheotomy.

Table 2-3: Characteristics of OTR flail chest patients who survived >24 hours by hospital discharge status

Characteristic (n)	Survivor group (n=985)	Mortality group (n=97)	p-value
Age (years) (n=1,082)	51.2 (50.1-52.2)	64.6 (61.0-68.2)	<0.0001
Sex (female) (n=1,082)	27.7% (24.9%-30.1%)	34.0% (24.7%-44.3%)	0.19
Proportion in 2004-2009 (n=1,082)	61.6% (58.5%-64.7%)	63.9% (53.5%-73.4%)	0.74
Systolic blood pressure (mm Hg) (n=1,055)	131.8 (130.0-133.6)	136.5 (129.6-143.4)	0.19
Hypertension (n=1,055)	40.2% (37.1%-43.3%)	44.3% (34.2%-54.8%)	0.45
Hypotension (n=1,055)	9.8% (8.0%-11.8%)	13.4% (7.3%-21.8%)	0.29
Heart rate (n=1,058)	97.3 (95.9-98.7)	96.3 (91.7-100.9)	0.69
Respiratory rate (n=699)	22.2 (21.6-22.7)	23.0 (20.4-25.5)	0.55
Positive BAC ^a (n=1,082)	13.5% (11.4%-15.8%)	10.3% (5.1%-18.1%)	0.43
Injury Severity Score (n=1,082)	31.4 (30.7-32.2)	39.1 (36.7-41.5)	<0.0001
Glasgow Coma Scale (n=950)	15 (15-15)	14 (12-15)	<0.0001
MAIS ^b (n=615)	3 (3-3)	5 (4-5)	<0.0001
Fractured ribs (n=633)			

1	1.4% (0.6%-2.7%)	1.8% (0.1%-9.6%)	0.65
2-4	15.6% (12.7%-18.8%)	17.9% (8.9%-30.4%)	
5+	83.0% (79.7%-86.0%)	80.4% (67.6%-89.8%)	
Comorbidities ^c (n=1,082)			
0	83.3% (80.8%-85.5%)	69.1% (58.9%-78.1%)	<0.001
1-2	15.2% (13.0%-17.6%)	23.7% (15.7%-33.4%)	
≥3	1.5% (0.9%-2.5%)	7.2% (3.0%-14.3%)	
Transfusion (n=1,082)	6.0% (4.6%-7.7%)	8.3% (3.6%-15.6%)	0.38
Definitive airway ^d (n=1,082)	38.4% (35.3%-41.5%)	70.1% (60.0%-79.0%)	<0.0001
Ventilation (n=1,082)	31.0% (28.1%-34.0%)	59.8% (49.4%-69.6%)	<0.0001
Chest tubes (n=1,082)	46.5% (43.4%-50.0%)	43.3% (33.3%-53.8%)	0.59
Thoracotomy (n=1,082)	0.5% (0.0%-0.1%)	2.1% (0.3%-7.3%)	0.12
CPR (n=1,082)	0.5% (0.0%-0.1%)	5.2% (1.7%-11.6%)	<0.001
Length of stay in special care unit (n=1,082)	6 (5-7)	7 (5-12)	<0.0051
Length of stay in hospital (n=1,073)	15 (14-16)	7 (6-15)	<0.001

^a Patient exceeded maximum legal blood alcohol limit for drivers in Ontario (i.e. 17.4 mmol/L or 0.08%).

^b Maximum Abbreviated Injury Score for the head and neck region.

^c Charlson and Elixhauser comorbidities were extracted from the ICD-9-CM and ICD-10 administrative codes using the Quan et al. (2005) coding algorithms. Comorbidities accounted for by both Charlson and Elixhauser methods were only counted once.

^d Definitive airway includes oral intubation, nasal intubation or tracheotomy.

Chapter 3

3 Logistic regression risk score for in-hospital mortality in 1,082 flail chest patients

3.1 Introduction

Flail chest is a severe type of rib fracture with an estimated mortality rate of 10% to 36% of cases (1-4). Operative repair of flail chest has been found to reduce length of stay in hospital and ICU, reduce in-hospital complications and improve long-term quality of life when compared to standard methods of care although it is considered to be underused likely because of uncertainty in optimal techniques and indications (5-12). Some studies have attempted to characterize mortality risk factors in flail chest but the findings are conflicting, the cut points vary, some information is not available before surgery (i.e. trauma scoring systems), some terms are too broadly defined (i.e. shock), and the clinical applications are unclear (13-19).

A risk score available before operative repair is needed to quantify individual risk of mortality in flail chest patients to inform surgeons considering operative repair. Patients at low to medium risk of mortality may be good candidates for operative repair and patients at high risk of mortality may not be suitable candidates since they are less likely to survive to benefit from operative repair (since randomized trials have not yet shown evidence that operative repair is a life-saving procedure) (8-10). Traditionally, logistic regression has been used to predict binary outcomes such as mortality and to generate scoring systems that can be applied at bedside by using a calculator, app, or computer. The objective of this study was to create a simple risk score using available preoperative covariates to calculate individual risk of mortality.

3.2 Methods

Data were available for 1,190 adult flail chest patients admitted to lead trauma hospitals from January 1, 1999, to March 31, 2009 and recorded as part of the Ontario Trauma Registry (OTR). The OTR was established in 1992 and its direct sources are the 11 lead trauma facilities in Ontario (20). They are mandated to report demographic, pre-hospital and hospital care, and patient outcomes on all adult hospitalizations due to major trauma (20). To be included in our study patients must have survived at least 24 hours after admission to lead trauma hospital which left 1,082 patients. There were 41 cases of operative repair of flail chest which were included and adjusted for in this analysis.

Model predictors were selected among 15 various patient characteristics (i.e. demographics, physiology, injury, procedures) between survivors and non-survivors of flail chest through independent t tests for continuous variables and Fisher's exact test for categorical variables adjusting for multiple testing using the Bonferroni correction (p-value was calculated as $p < 0.003$ after $p < 0.05$ was divided by 15 variable comparisons). Definitive airway was defined as oral or nasal intubation or tracheotomy. Mechanical ventilation included both invasive and noninvasive cases (i.e. continuous positive airway pressure (CPAP) given via a face mask, intermittent positive pressure ventilation (IPPV) with endotracheal intubation, etc.). Patients who underwent intubation in order for ventilation to be administered would be counted twice by the model. Year of hospital admission and if operative repair was performed were also investigated as potential confounders. Glasgow Coma Scale was the sole parameter containing missing observations. There were 132 (12.2%) missing observations for GCS. Logistic regression was therefore modeled three ways to account for possible biases due to missing observations including selection bias, confounding, and lack of generalizability respectively: a model excluding missing data (i.e. complete case analysis), a model excluding GCS as a predictor, and a model including multiple imputation for missing observations of GCS. Multiple imputation was performed using a fully conditional specification approach, which has been shown to provide good coverage even in non-normal parameters such as GCS; and used 40 imputations, which has been recommended to prevent power falloff (21-22). The endpoint was all-cause in-hospital mortality.

The study followed the suggested modelling strategy of Harrell et al. (23) using the entire dataset to train the model. Component plus residual plots were evaluated to determine if the model met linearity assumptions. Pre-determined interactions included in the model were age by GCS, age by definitive airway and age by ventilation. These interaction terms were chosen because age is known to be a strong risk factor for death and there was enough variation in GCS, definitive airway and ventilation to make a study of these possible interactions relevant. A pre-specified subset of predictors were tested for significance including the three interaction terms and two possible confounders (age by GCS, age by ventilation, age by definitive airway, year of hospital admission and if operative repair was performed). If a predictor was not significant but had an odds ratio greater than or equal to 1.2 it was allowed to remain in the model since these predictors contribute to model performance (24).

The final model was validated for calibration and discrimination. Calibration refers to how well the observed outcome and predicted outcome agree and can be assessed with the Hosmer-Lemeshow goodness of fit test (25). Discrimination refers to how well the model can separate patients at high risk of death and patients at low risk of death and is given by area under the receiver operating characteristic curve (c index) (25-26). A good or excellent predictive model would have a c index above 0.8, a moderately discriminating model would have a c index between 0.7 and 0.8, and a low discriminating model would have a c index between 0.6 and 0.7 (25).

Predictive models tend to perform better in the training data set than in new data sets; therefore to determine the expected model performance in new patients at similar risk of mortality, the optimism-corrected c index was calculated (23). The c index was calculated for the final model in the original sample and was compared to the c indexes calculated in bootstrap samples. Bootstrapping was performed by generating 400 random samples of equal size as the original sample with replacement from the original sample. The average difference between the c index calculated using the original sample and the c indexes calculated using bootstrap samples represents the optimism of the model (23). All analysis was conducted using SAS software, version 9.4 (SAS Institute, Inc, Cary, NC).

Bootstrapping was conducted using SAS Enterprise Miner version 12.3 (SAS Institute, Inc, Cary, NC).

The odds ratios and c index of the final Model 1 were compared to the other two models used to address the missing values. A plot displaying the predicted and observed probability of risk across the deciles of risk for Model 1 is provided in Figure 5.

Risk scores for mortality were calculated using the method developed to produce the Charlson Comorbidity Index where a whole number point is assigned based on the odds ratio of a risk factor (27). In this method, if the odds ratio is equal to or greater than 1.2 but less than 1.5, 1 point is assigned; for odds ratios equal to or greater than 1.5 but less than 2.5, 2 points are assigned; for odds ratios equal to or greater than 2.5 but less than 3.5, 3 points are assigned and so forth. For odds ratios less than one, the inverse was taken so that positive point values were always assigned. A plot displaying the number of points and observed mortality is provided in Figure 6.

3.3 Results

Characteristics of the survivors and non-survivors are given in Table 3-1. The mean age of the 1,082 flail chest patients was 47.6 ± 17.1 (\pm SD) years. Over 70% of the flail chest patients were male and there was no evidence of a significant difference in survival between sexes ($p=0.19$). There was no evidence of a significant difference in systolic blood pressure, heart rate, respiratory rate, blood alcohol, number of fractured ribs, transfusions, chest tubes or thoracotomies ($p>0.05$). The median Glasgow Coma Scale was 15. Ten flail chest patients (<1%) had CPR. There were 446 (41.2%) patients who required a definitive airway procedure (2 patients required tracheotomies at the primary and later at the lead trauma hospital, 21 patients required nasal intubation, 421 patients required oral intubation, 2 patients required a nasal and oral intubation). Approximately one third (33.6%) of flail chest patients required ventilation. One hundred and ninety-five flail chest patients (18.0%) had at least one comorbidity. Seventy-seven of the 950 (8.1%) patients included in the complete case analysis died.

There was no evidence of confounding by year of lead trauma hospital admission and operative repair ($p=0.80$ and $p=0.98$ respectively). Age by ventilation and age by definitive airway were not significant interactions ($p=0.70$ and $p=0.97$ respectively). Age by GCS was a significant interaction ($p=0.0035$). The age by GCS interaction suggested that a lower GCS was protective for mortality in older adults, which is contrary to what would be clinically expected. It was determined that the parameter estimates of a model excluding this interaction were correlated 98% and that there was no real difference in c indexes (c index 0.863 with interaction vs c index 0.853 without interaction) so the interaction terms and confounders were excluded from the final model. The final model estimates for Model 1 are provided in Table 3-2. The largest risk factors were definitive airway (OR 2.38), age (OR 2.00), and CPR (OR 1.89). Ventilation, CPR, and number of comorbidities did not reach statistical significance however the odd ratios of their effects were large enough that they contributed to the model performance so they remained in the final model.

The Hosmer-Lemeshow test indicated no evidence of a lack of fit in Model 1 suggesting good model calibration ($p=0.14$). The c index for Model 1 in the original sample was 0.853 and the optimism-corrected c index was 0.828 suggesting the model performs well in new patients. The receiver operating curve for Model 1 is shown in Figure 4.

The parameter estimates and c indexes for the three models for addressing missing values are compared in Table 3-3. The best discriminating model is the complete case analysis including GCS and parameter estimates with the exception of CPR do not vary much between models.

Figure 5 shows the observed and predicted probabilities of death across deciles of risk for Model 1. The observed and predicted probabilities of death tend to increase with higher rankings of predicted risk of death.

Figure 6 shows the incidence of mortality by number of assigned points. Less than 6 points is consistent with <2% observed mortality, six to 12 points is consistent with <10% mortality, 12 to 14 points is consistent with 27% mortality and 15 or more points is

consistent with 45% mortality. Using this point system most (87.2%) of the sample would have a predicted risk of mortality less than ten percent.

The excel formulas for the logistic regression in-hospital mortality risk scoring system can be found in Appendix H.

3.4 Discussion

We have developed a risk score using logistic regression for surgeons considering operative repair of flail chest using a trauma dataset from the largest province in Canada. Scoring flail chest patients using a points system based on our internally validated model combines mortality risk factors to determine individual risk of death (Hosmer-Lemeshow test $p=0.14$, optimism-corrected c index=0.828). Trauma surgeons can use the risk score to screen potential candidates for operative repair based on the candidate's likelihood to survive to benefit from the procedure. Patients at low to medium risk of mortality may be good candidates for operative repair and patients at high risk of mortality may not be suitable candidates since they are less likely to survive to benefit from operative repair (since randomized trials have not yet shown evidence that operative repair is a life-saving procedure) (8-10). This is a novel method of identifying flail chest patients eligible for operative repair.

Our results showed that mortality may be accurately predicted from six risk factors that are easily obtained during the initial assessment of the trauma patient: age, GCS, ventilation, definitive airway, CPR and number of comorbidities. The predicted risk of mortality was consistent with observed mortality for all levels of risk. The optimism-corrected c index of 0.828 indicated excellent predictive performance in new patients at similar risk (17). A comparison of the three models (complete case analysis, removing variables with missing values from the model, multiple imputation) suggests that the parameters were well described in the first model indicating minimal selection bias due to missing observations with the possible exception of CPR which may have been underestimated in the complete case analysis model. Despite the fact that CPR was observed in less than one percent of the study sample population and may have been

underestimated in the model, we chose to keep it in the model since it is easily determined in a patient's charts, it contributed to model performance and it is a marker of injury severity.

One limitation is that the only outcome that the model addressed was in-hospital mortality. There may be other outcomes of interest to surgeons such as long-term quality of life, length of stay in intensive care unit and in hospital, and ventilator-free days. Future research evaluating some of these outcomes would require additional data since quality of life information (including pain) and ventilator-free days were either not available or not easily available in the OTR. However, all-cause mortality can be measured without error and is perhaps the most important outcome from a patient perspective. Additionally this model was constrained by the number of parameters and by the completeness of the data collected by the Ontario Trauma Registry. There are potentially other important survival factors such as pulmonary contusion and other complications which we chose not to analyze because the database could only indicate if these existed; not to what extent. However, since severe pulmonary complications resulting in respiratory failure (including pulmonary contusion) are treated with mechanical ventilation, including mechanical ventilation in the model will serve as a marker to account for (at least to some extent) these complications. Also, it was not possible from the database to distinguish bilateral and unilateral flails or which type of mechanical ventilation was administered (invasive or noninvasive). There were also missing values for GCS which we attempted to account for using three separate modeling strategies. Furthermore, the model was calculated using data from lead trauma hospitals in Ontario and may not be appropriate in areas outside Ontario. Prospective validation in and extending beyond Ontario is recommended before the risk score can be widely implemented. Finally, larger randomized trials may yet show evidence that operative repair of flail chest is a life-saving procedure, therefore patients with high risk scores for mortality may one day be prioritized for operative repair rather than excluded from it (8-10). Current evidence may be inadequate to guide how to best interpret risk scores. Our hope is that the risk score may be a tool to motivate further research and guide policy-making in screening patients for operative repair.

3.5 Conclusions

This was the first study to examine the risk of in-hospital mortality in flail chest patients. We have developed a simple model which can be easily applied at bedside by accessing a spreadsheet program in an app or other handheld computer device. The model uses six risk factors that are readily obtained during the initial assessment of the trauma patient: age, GCS, ventilation, definitive airway, CPR and number of comorbidities. It was determined that <6 points is consistent with <2% observed mortality, six to 12 points is consistent with <10% mortality, 12 to 14 points is consistent with 27% mortality and 15 or more points is consistent with 45% mortality. Using this point system most (87.2%) of the sample would have a predicted risk of mortality less than ten percent. This model has the potential to be a useful tool for surgeons considering operative repair of flail chest.

3.6 References

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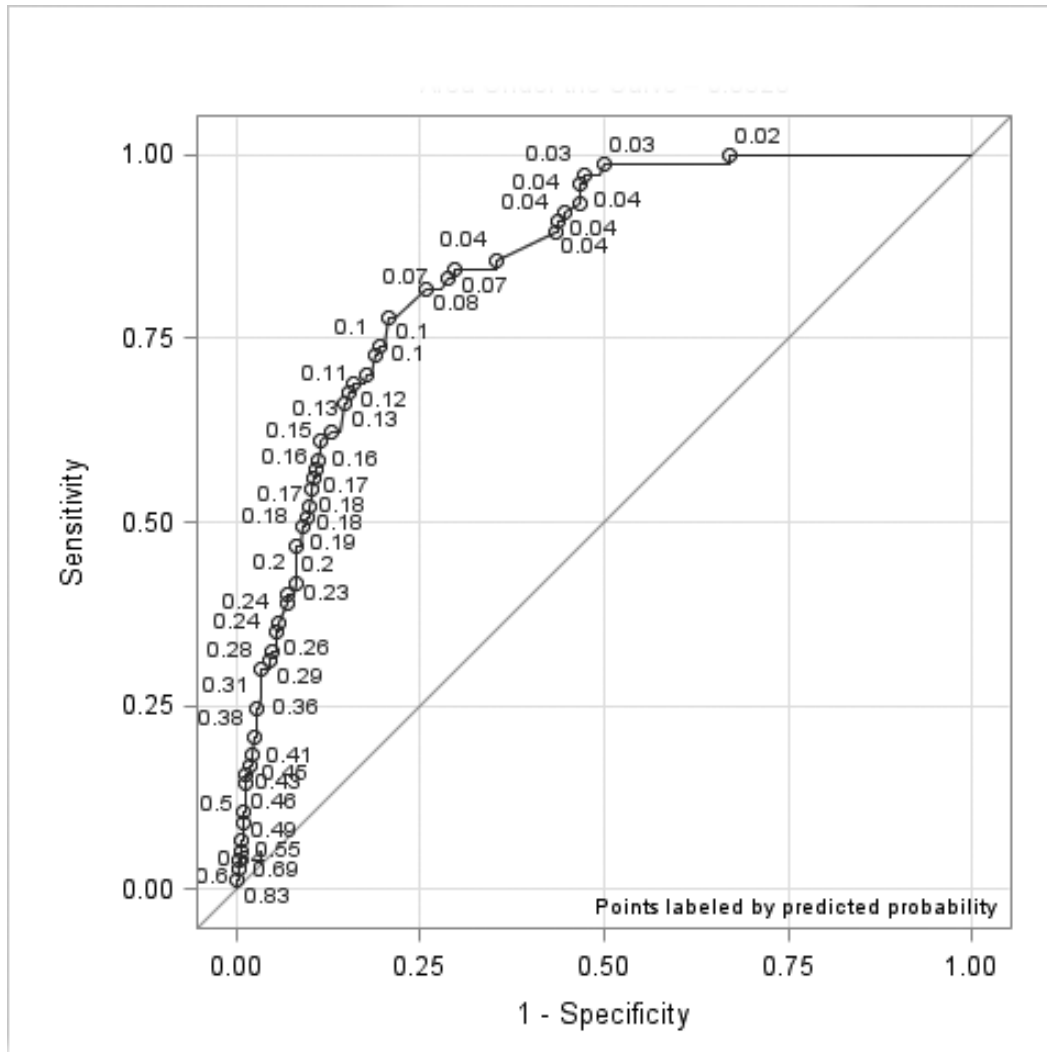


Figure 4: Receiver operating characteristic curve for Model 1

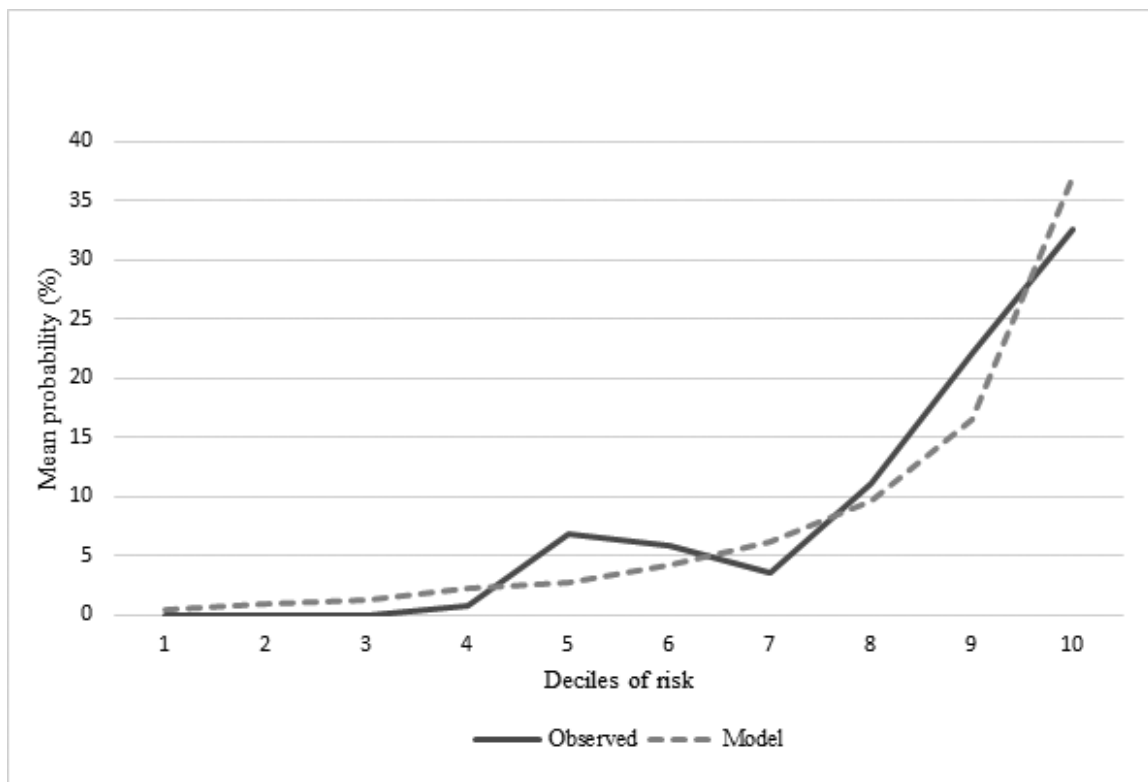


Figure 5: Observed and predicted mortality in flail chest

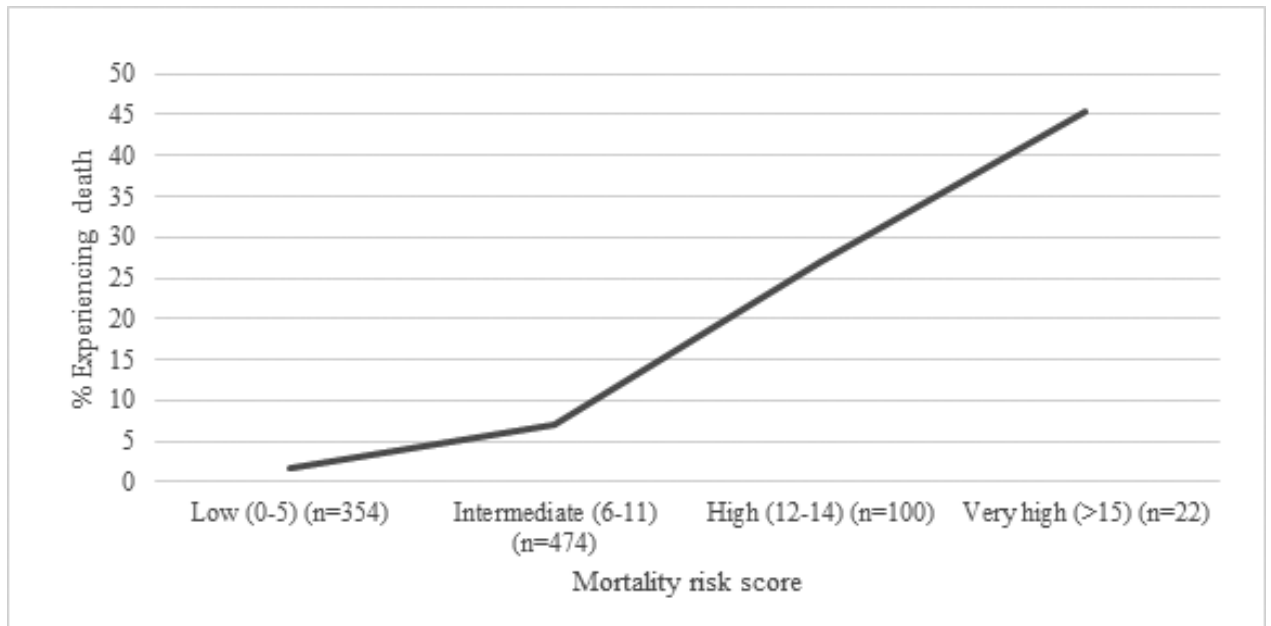


Figure 6: Observed mortality by risk score in flail chest

Table 3-1: Characteristics of OTR flail chest patients who survived >24 hours by hospital discharge status

Characteristic	All patients (n=1,082)	Survivor group (n=985)	Mortality group (n=97)	p-value
Age (years) (mean \pm SD)	52.4 (\pm 17.0)	51.2 (\pm 16.4)	64.6 (\pm 17.8)	<0.0001
Sex (male)	776 (71.7%)	712 (72.3%)	64 (66.0%)	0.19
Systolic blood pressure (mm Hg) (mean \pm SD)	132.2 (\pm 28.9)	131.8 (\pm 28.5)	136.5 (\pm 33.0)	0.19
Heart rate (mean \pm SD)	97.2 (\pm 22.2)	97.3 (\pm 22.2)	96.3 (\pm 22.6)	0.69
Respiratory rate (mean \pm SD)	22.2 (\pm 6.9)	22.2 (\pm 6.9)	23.0 (\pm 8.1)	0.55
Positive BAC ^a	143 (13.2%)	133 (13.5%)	10 (10.3%)	0.43
Glasgow Coma Scale (median)	15	15	14	<0.0001
Fractured ribs				
1	9 (1.4%)	8 (1.4%)	1 (1.8%)	0.65
2-4	100 (15.8%)	90 (15.6%)	10 (17.9%)	
5+	524 (82.8%)	479 (83.0%)	45 (80.3%)	
Number of	0	0	0	<0.001

comorbidities ^b (median)				
Transfusion	67 (6.2%)	59 (6.0%)	8 (8.3%)	0.38
Chest tubes	500 (46.2%)	458 (46.5%)	42 (43.3%)	0.59
Thoracotomy	7 (0.7%)	5 (0.5%)	2 (2.1%)	0.12
Definitive airway ^c	446 (41.2%)	378 (38.4%)	68 (70.1%)	<0.0001
Ventilation	363 (33.6%)	305 (31.0%)	58 (59.8%)	<0.0001
CPR	10 (0.9%)	5 (0.5%)	5 (5.2%)	<0.001

^a Patient exceeded maximum legal blood alcohol limit for drivers in Ontario (i.e. 17.4 mmol/L or 0.08%).

^b Charlson and Elixhauser comorbidities were extracted from the ICD-9-CM and ICD-10 administrative codes using the Quan et al. (2005) coding algorithms. Comorbidities accounted for by both Charlson and Elixhauser methods were only counted once.

^c Definitive airway includes oral intubation, nasal intubation or tracheotomy.

Table 3-2: Odds ratios and points for Model 1 predictors

Predictor	Odds ratio (95% CI)	Points ^a	p value
Age (per 10 years after age 20)	2.00 (1.67, 2.39)	2	<0.0001
GCS (per two score drop from 15)	1.25 (1.14, 1.35)	1	<0.0001
Ventilation (vs. no ventilation)	1.42 (0.67, 3.02)	1	0.3563
Definitive airway (vs. no definitive airway)	2.38 (1.11, 5.09)	2	0.0252
CPR (vs. no CPR)	1.89 (0.40, 9.06)	2	0.4239
Number of comorbidities	1.25 (0.94, 1.67)	1	0.1314

^a Points were calculated using the method described by Charlson et al. (1997)

Table 3-3: Odds ratios (95% CI) and model performances for three missing values models

	Model 1: Complete case analysis	Model 2: Excluding GCS	Model 3: Multiple imputation for GCS
GCS	0.75 (0.65, 0.86)	XX	0.75 (0.66, 0.86)
Age	2.00 (1.67, 2.39)	1.67 (1.45, 1.93)	1.75 (1.51, 2.04)
Definitive airway	2.38 (1.11, 5.09)	2.98 (1.48, 6.00)	2.33 (1.16, 4.69)
Ventilation	1.42 (0.67, 3.02)	1.62 (0.83, 3.17)	1.32 (0.68, 2.58)
CPR	1.89 (0.40, 9.06)	5.62 (1.47, 21.43)	4.06 (1.04, 15.88)
Comorbidity count	1.25 (0.94, 1.67)	1.42 (1.11, 1.83)	1.40 (1.09, 1.82)
C index	0.853	0.805	0.834

Chapter 4

4 Decision tree risk score: a better tool for predicting in-hospital mortality in flail chest than logistic regression?

4.1 Introduction

Operative repair of flail chest remains a rarely used procedure despite evidence that it is superior with respect to time on ventilation, time in ICU, rate of ventilator-associated pneumonia and rate of tracheostomy when compared to standard methods of care; probably due to uncertainty in optimal techniques and indications (1-8). With the myriad of potential surgical indications, a wiser approach of selecting these patients may be to use a risk score which is capable of integrating risk factors and providing a summary score. Some studies have attempted to characterize mortality risk factors in flail chest but the findings are conflicting, the cut points vary, some information is not available before surgery (i.e. trauma scoring systems), some terms are too broadly defined (i.e. shock), and the clinical applications are unclear (9-15).

Traditionally, logistic regression has been used to predict binary outcomes such as mortality. The objective of our study was to develop a decision tree that could be used as a risk score to predict in-hospital mortality in flail chest patients using routinely measured, preoperative covariates. Decision trees have several advantages including ease of interpretation, ability to be trained on small data samples, direct derivation of decision rules, robustness to irrelevant information, and usage of all data (including missing values) (16). The results of the decision tree model were compared to previous logistic regression analysis, which used the same flail chest sample population and predictors, to assess overall model performance and consistency of results (17).

4.2 Methods

All statistical analysis was conducted using SAS Enterprise Miner version 12.3 (SAS Institute, Inc, Cary, NC). There were 1,190 flail chest patients in the Ontario Trauma

Registry (January 1, 1999, to March 31, 2009). The Ontario Trauma Registry was established in 1992 and its direct sources are the 11 lead trauma facilities in Ontario. They are mandated to report demographic, pre-hospital and hospital care, and patient outcomes on all adult hospitalizations due to major trauma (18). To be included in our study patients must have survived at least 24 hours after admission to lead trauma hospital which left 1,082 patients. The outcome was in-hospital mortality. There were 41 cases of operative repair of flail chest which were not excluded from analysis. To account for possible differences in results between flail chest patients who underwent operative repair and flail chest patients who did not, decision trees were crafted for all flail chest patients and for all flail chest patients who did not undergo operative repair. Any large discrepancies between the trees would suggest that operative repair alters the patient's risk of mortality enough to displace the risk grouping the patient would have been assigned had he/she not undergone operative repair.

Partitioning variables were selected among 15 various patient characteristics (i.e. demographics, physiology, injury, procedures) between survivors and non-survivors of flail chest through independent t tests for continuous variables and Fisher's exact test for categorical variables adjusting for multiple testing using the Bonferroni correction (p-value was calculated as $p < 0.003$ after $p < 0.05$ was divided by 15 variable comparisons). Definitive airway was defined as oral or nasal intubation or tracheotomy. Mechanical ventilation included both invasive and noninvasive cases (i.e. continuous positive airway pressure (CPAP) given via a face mask, intermittent positive pressure ventilation (IPPV) with endotracheal intubation, etc.). Patients who underwent intubation in order for ventilation to be administered would be counted twice by the model. Glasgow Coma Scale was the only parameter with missing observations. There were 132 (12.2%) missing observations for GCS.

A Classification and Regression Tree decision tree uses an approach called "recursive partitioning" to generate homogeneous risk groups (19). When a split occurs two groups are formed where a case with the input value less than the split would fall into one group and a case with an input value greater than the split would fall into the other group (20). If there are subjects that are missing values for the splitting variable, then these subjects

are added to the risk group that creates the best split (20). The splitting process was performed for each of the inputs and the biggest logworth was taken as the first split (20). Predictors were only used once in the same series of splits in the decision tree (i.e. a predictor which had already been used to split a risk group could not be re-used later in that same risk group). Recursive partitioning continued until a set stopping criterion ended the process (20). In our study the stopping criterion was a minimum number of ten observations in a daughter node. Ten was chosen because it represented approximately one percent of the sample size and risk groups of less than one percent of the sample can be assumed to be too atypical to be relevant in practice.

The decision tree was validated for calibration and discrimination. Calibration here refers to the proportion of outcomes correctly classified by the decision tree and is known as the tree classification accuracy (22). Discrimination refers to how well the model can separate patients at high risk of death from patients at low risk of death (21). It is calculated by the c index which is equivalent to the area under the receiver operating curve (ROC curve) (21). A good or excellent predictive model would have a c index above 0.8, a moderately discriminating model would have a c index between 0.7 and 0.8, and a low discriminating model would have a c index between 0.6 and 0.7 (21).

The c index and classification accuracy were calculated for three decision tree strategies: a decision tree trained on the original sample (Model 1), a decision tree trained on the original sample excluding cases of operative repair (Model 2) and finally for ten decision trees trained on random samples of 90% of the original sample, stratified by mortality and pooled to form an average (Model 3). Random subsamples drawn without replacement enable reliable interpretation of risk grouping importance and estimate the misclassification that would arise from a new population at similar risk for the outcome (19, 22). The splitting variables included in the ten decision trees and their importance are provided as an indication of model stability in similar risk populations.

Finally the importance that the decision tree assigned to the predictors and model discrimination were compared to the results of previous logistic regression to assess the relative value of the decision tree methodology. The logistic regression model was

generated from the same data set and predictors as the decision trees and the final logistic regression model did not include any interactions or confounders (17).

4.3 Results

Characteristics of the survivors and non-survivors are given in Table 4-1. There were 97 deaths (9.0%) of the 1,082 flail chest patients. Mean age was 47.6 ± 17.1 (\pm SD) years. The median Glasgow Coma Scale was 15. Ten flail chest patients (<1%) had cardiopulmonary resuscitations (CPR). There were 446 (41.2%) patients who required a definitive airway procedure (2 patients required tracheotomies at the primary and later at the lead trauma hospital, 21 patients required nasal intubation, 421 patients required oral intubation, 2 patients required a nasal and oral intubation). Approximately one third (33.6%) of flail chest patients required ventilation. One hundred and ninety-five flail chest patients (18.02%) had at least one comorbidity.

As shown in Figure 7, there were five mortality risk groups identified by the decision tree. Flail chest patients of 70 or more years of age with a Glasgow Coma Scale less than 11 were at greatest risk of mortality (52.94%) and they represented 1.57% of the sample population. The next highest mortality risk group was flail chest patients of 70 or more years of age with a Glasgow Coma Scale greater than or equal to 11 and their risk was 20.65% and they represented 17.01% of the sample population. Flail chest patients younger than 70 years of age but with a Glasgow Coma Scale less than 8 were at similar risk of mortality as patients of 70 or more years of age with a high GCS (16.93%) and they represented 17.47% of the sample population. Patients at lower risk of mortality (7.19%) were younger than age 70 with a Glasgow Coma Scale of 8 or greater and required a definitive airway and they represented 18.39% of the sample population. Under half of the sample population (45.56%) had the lowest risk of mortality (1.01%) and they included flail chest patients younger than age 70, with a Glasgow Coma Scale of 8 or greater and did not a definitive airway. The two most significant predictors of in-hospital death were age and Glasgow Coma Scale. Definitive airway was found to be a significant predictor of in-hospital death in 63.96% of cases (692 of 1,082 flail chest cases).

Table 4-2 lists the misclassification rates, classification accuracies, and c-indexes for the three models. The decision tree excluding cases of operative repair and the decision trees trained on stratified random samples can be found in the Appendix H. The results were highly consistent suggesting that operative repair was not a strong determinant of mortality risk and that the model can be expected to perform similarly in new patients at similar mortality risk.

Figure 8 shows the predictors used to partition the ten validation subsamples into risk groups and their importance (or position in the hierarchy of the tree). Age was always used to make the first partition. Glasgow Coma Scale (GCS) was always the second partitioning predictor. Definitive airway was often used in the third partition of risk groups although which risk groups were split varied between subsamples. Ventilation was a third partitioning predictor in eight of the ten subsamples. Number of comorbidities was used as both a third partitioning predictor and a fourth partitioning predictor. Three decision trees used number of comorbidities twice to split risk groups in different series. CPR was never used to partition risk groups.

Table 4-3 compares the results of previous logistic regression to the decision tree results. The logistic regression analysis showed better discrimination and placed different importance on predictors (as determined by the magnitude of the odds ratios) than the decision tree methodology with the exception of age and GCS which were ranked as the two most important predictors of mortality.

4.4 Discussion

We developed and validated a province-wide risk score for surgeons selecting patients for operative repair of flail chest. Risk grouping using the decision tree approach has been shown to have excellent calibration and moderate discrimination (20). Trauma surgeons can use the risk score to screen potential candidates for operative repair based on the candidate's likelihood to survive to benefit from the procedure. Patients at low to medium risk of mortality may be good candidates for operative repair and patients at high risk of mortality may not be suitable candidates since they are less likely to survive to benefit from operative repair (since randomized trials have not yet shown evidence that operative

repair is a life-saving procedure) (4-6). This is a novel method of identifying flail chest patients eligible for operative repair.

Our study was based on one of the largest samples of flail chest patients available in the literature to date. Its results showed that mortality may be accurately predicted from three risk factors (age, GCS and definitive airway) that are already collected by the hospital and uses patient and clinical data available before operative repair (c-index 0.796). The decision trees excluding operatively repaired patients and including operatively repaired patients are highly similar which suggests that the procedure does little to change a patient's risk of mortality. The pooled results of the validation subsamples indicate the expected model discrimination in similar risk populations is excellent. The variables involved in recursive partitioning of the OTR sample and their importance were consistent across the validation subsamples which suggests the model performs reliably in similar risk populations.

The decision tree discriminates well but not as well as logistic regression. One possible explanation for this is that decision trees categorize continuous variables which causes a loss of information. Also, the decision tree model was stopped when node size reached approximately 1% of the study sample and as such accounted for fewer risk factors than logistic regression. Allowing the model to continue to unrestrainedly partition the data would allow for the inclusion of more patient information but would increase the risk of overfitting the model. Interestingly, the decision tree identified the highest at-risk subgroup in the OTR as patients of 70 or more years of age with a GCS of ten or lower. Using the points system generated by logistic regression, this subgroup would have at least twelve points which represents approximately 27% risk. However, the decision tree characterizes the risk of mortality as 52.9% in this subgroup, which is considerably higher than 27%. This suggests that either the decision tree analysis overestimated risk in some subgroups or that logistic regression underestimated risk in some subgroups. Because there were so few patients in the highest risk deciles, it is difficult to determine using these data which is the case. However, a recent study found that logistic regression was less likely than a decision tree to underestimate risk suggesting that it is more probable that the decision tree overestimated risk (23). We propose that because the

logistic regression model was more discriminate, included more patient information, and may be less likely to overestimate risk in some subgroups, that the logistic regression model may be a better risk model for calculating risk of in-hospital mortality in flail chest patients.

One limitation is that the only outcome that the model addressed was in-hospital mortality. There may be other outcomes of interest to surgeons such as long-term quality of life, length of stay in intensive care unit and in hospital, and ventilator-free days. Future research evaluating some of these outcomes would require additional data since quality of life information (including pain) and ventilator-free days were either not available or not easily available in the OTR. However, all-cause mortality can be measured without error and is perhaps the most important outcome from a patient perspective. Additionally this model was constrained by the number of parameters and by the completeness of the data collected by the Ontario Trauma Registry. There are potentially other important survival factors such as pulmonary contusion and other complications which we chose not to analyze because the database could only indicate if these existed; not to what extent. However, since severe pulmonary complications resulting in respiratory failure (including pulmonary contusion) are treated with mechanical ventilation, including mechanical ventilation in the model will serve as a marker to account for (at least to some extent) these complications. Also, it was not possible from the database to distinguish bilateral and unilateral flails or which type of mechanical ventilation was administered (invasive or noninvasive). There were also missing values for GCS in the OTR dataset but these were included during the model partitioning. Fourthly, the model was calculated using only data from lead trauma hospitals in Ontario and may not be appropriate in areas outside Ontario. External validation of the model outside of Ontario is recommended. Additionally, the cut point of a decision tree can be very sensitive to small changes in the training set which means surgeons should not strictly adhere to the cut points presented in our study but rather use them judiciously when calculating mortality risk (19). Finally, larger randomized trials may yet show evidence that operative repair of flail chest is a life-saving procedure, therefore patients with high risk scores for mortality may one day be prioritized for operative repair rather than excluded from it (4-6). Current evidence may be inadequate

to guide how to best interpret risk scores. Our hope is that the risk score may be a tool to motivate further research and guide policy-making in screening patients for operative repair.

Conclusions

This was the first study to examine the risk of in-hospital mortality in flail chest patients using decision tree methodology and has used one of the largest samples of flail chest patients in the literature to date. The decision tree model calculates risk using three patient characteristics (age, GCS, definitive airway) and appears to be a valid predictor of in-hospital mortality risk in flail chest. However, it seems to be less useful than the logistic regression model at predicting mortality risk. This model has the potential to be a useful tool for surgeons for selecting patients for operative repair of flail chest.

4.5 References

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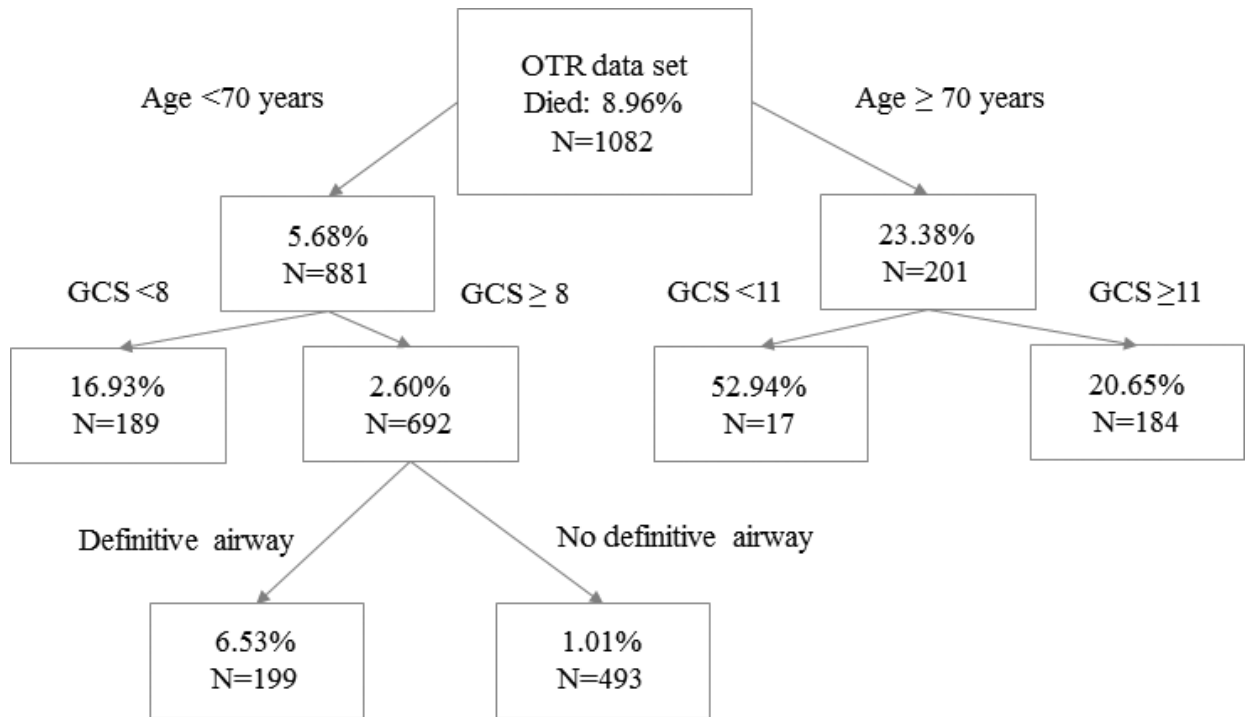


Figure 7: Decision tree analysis for in-hospital mortality of flail chest

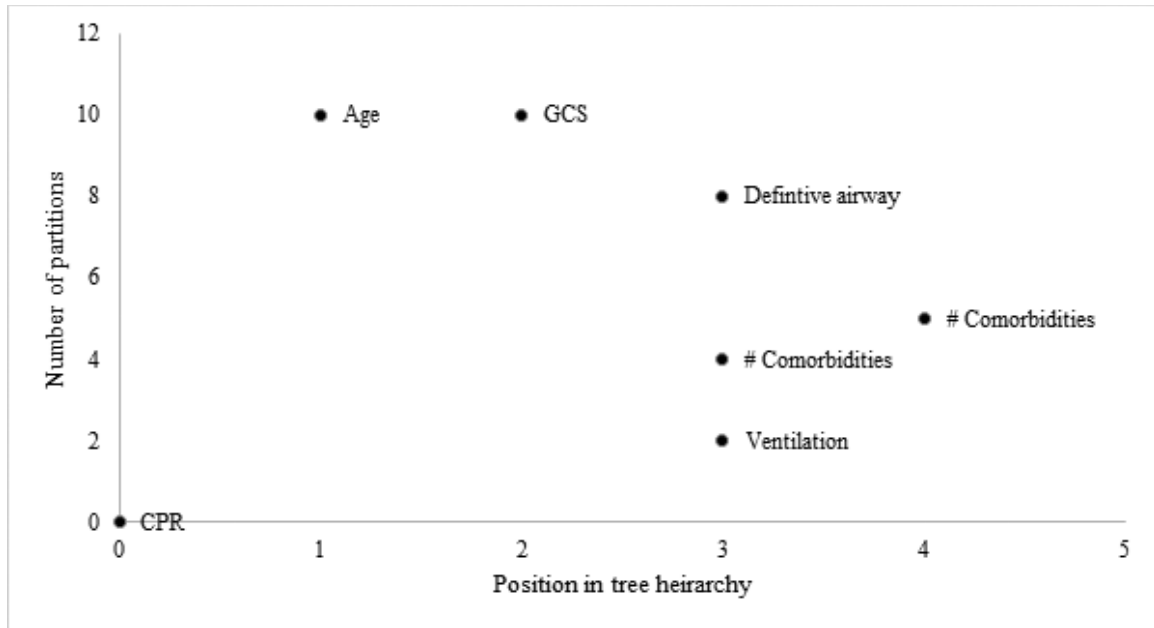


Figure 8: Predictor importance in ten subsamples

Table 4-1: Characteristics of OTR flail chest patients who survived >24 hours by hospital discharge status

Characteristic	All patients (n=1,082)	Survivor group (n=985)	Mortality group (n=97)	p-value
Age (years) (mean \pm SD)	52.4 (\pm 17.0)	51.2 (\pm 16.4)	64.6 (\pm 17.8)	<0.0001
Sex (male)	776 (71.7%)	712 (72.3%)	64 (66.0%)	0.19
Systolic blood pressure (mm Hg) (mean \pm SD)	132.2 (\pm 28.9)	131.8 (\pm 28.5)	136.5 (\pm 33.0)	0.19
Heart rate (mean \pm SD)	97.2 (\pm 22.2)	97.3 (\pm 22.2)	96.3 (\pm 22.6)	0.69
Respiratory rate (mean \pm SD)	22.2 (\pm 6.9)	22.2 (\pm 6.9)	23.0 (\pm 8.1)	0.55
Positive BAC ^a	143 (13.2%)	133 (13.5%)	10 (10.3%)	0.43
Glasgow Coma Scale (median)	15	15	14	<0.0001
Fractured ribs				
1	9 (1.4%)	8 (1.4%)	1 (1.8%)	0.65
2-4	100 (15.8%)	90 (15.6%)	10 (17.9%)	
5+	524 (82.8%)	479 (83.0%)	45 (80.3%)	
Number of	0	0	0	<0.001

comorbidities ^b (median)				
Transfusion	67 (6.2%)	59 (6.0%)	8 (8.3%)	0.38
Chest tubes	500 (46.2%)	458 (46.5%)	42 (43.3%)	0.59
Thoracotomy	7 (0.7%)	5 (0.5%)	2 (2.1%)	0.12
Definitive airway ^c	446 (41.2%)	378 (38.4%)	68 (70.1%)	<0.0001
Ventilation	363 (33.6%)	305 (31.0%)	58 (59.8%)	<0.0001
CPR	10 (0.9%)	5 (0.5%)	5 (5.2%)	<0.001

^a Patient exceeded maximum legal blood alcohol limit for drivers in Ontario (i.e. 17.4 mmol/L or 0.08%).

^b Charlson and Elixhauser comorbidities were extracted from the ICD-9-CM and ICD-10 administrative codes using the Quan et al. (2005) coding algorithms. Comorbidities accounted for by both Charlson and Elixhauser methods were only counted once.

^c Definitive airway includes oral intubation, nasal intubation or tracheotomy.

Table 4-2: Decision tree model performances

	Misclassification rate	Classification accuracy	C-index
Model 1: Original OTR sample	0.089	91.1%	0.796
Model 2: OTR sample excluding cases of operative repair	0.092	90.8%	0.814
Model 3: Pooled subsample results	0.089	91.1%	0.810

Table 4-3: Comparison of decision tree and logistic regression results*: ranking of predictor importance and model discrimination

	Age	GCS	Definitive airway	Ventilation	Number of comorbidities	CPR	C index
Logistic regression	1	2	1	2	2	1	0.853
Decision tree	1	2	3	3	3,4	Never assigned	0.796

*Ranking for logistic regression was based on the magnitude of the risk factor odds ratios (15).

Chapter 5

5 Discussion

5.1 Characteristics of flail chest patients operatively repaired in Ontario, Canada

The results from Chapter Two found no evidence of a statistically significant difference in mortality between patients operatively repaired and those who were not. This suggests that operative repair in flail chest patients is not a life-saving procedure. This is consistent with the findings of the three randomized controlled trials evaluating the efficacy of operative repair in flail chest patients (1-3).

Also, Chapter Two found no evidence of any statistically significant differences with regards to demographics, injuries, procedures and mortality between operatively repaired patients and non-operatively repaired patients which was surprising given that certain patient characteristics are considered unfavorable for surgery (4). This could be explained by the current uncertainty in who should be considered for operative repair (5).

The OTR flail chest patients included in the study were similar to the NTDB flail chest patients with respect to age and sex (6). The OTR flail chest patients had lower rates of ventilation than NTDB flail chest patients (33.6% vs 59%), OTR operatively repaired flail chest patients had higher rates of chest tubes than NTDB flail chest patients (57.1% vs 44%), and the mortality rate for all OTR flail chest patients was lower than NTDB flail chest patients (9.0% vs 16%) (6).

Chapter Two identified several mortality risk factors including age, ISS, GCS, MAIS, number of comorbidities, definitive airway, ventilation, and CPR: of these only ISS and MAIS are not available before operative repair (7). Results confirmed that age, ISS, GCS, number of comorbidities and ventilation may be risk factors for mortality in flail chest patients (8-11). Our study did not find evidence that number

of rib fractures or blood transfusion are significantly associated with mortality but did newly identify CPR and definitive airway as new risk factors (4, 8-11).

5.2 Logistic regression model for predicting in-hospital mortality in flail chest patients

Chapter Three found that in-hospital mortality in cases of flail chest can be accurately predicted from six risk factors that are already collected by the hospital and available before operative repair: age, GCS, number of comorbidities, definitive airway, ventilation and CPR. This makes the scoring system valuable since existing trauma scoring systems (i.e. ISS, RTS, APACHE, TRISS) that predict mortality are not available at the time of operative repair and so cannot be used at bedside (7).

The risk of mortality predicted by the model was consistent with observed mortality for all levels of risk however because there were few patients in the highest deciles of risk this should be interpreted cautiously. The optimism-corrected c index (c index 0.828) indicated excellent predictive performance in new patients at similar risk (12). A comparison with different modeling strategies accounting for missing values (including complete case analysis, removing variables with missing values, and multiple imputation) suggested minimal selection bias (with the possible exception of CPR) associated with the complete case analysis approach. Because CPR was performed in less than 1% of the study sample it could be argued that it is not a very important risk factor however surgeons should be warned that the mortality risk for patients who did receive CPR may be higher than what was calculated by the model.

5.3 Decision tree model for predicting in-hospital mortality in flail chest patients

Chapter Four found that in-hospital mortality in cases of flail chest can also be accurately predicted from only three risk factors that are already collected by the hospital and available before operative repair: age, GCS and definitive airway. This makes the scoring system valuable since existing trauma scoring systems (i.e. ISS, RTS, APACHE, TRISS)

that predict mortality are not available at the time of operative repair and so cannot be used at bedside (7).

Compared to logistic regression, the decision tree discriminates well but not as well as logistic regression. One possible explanation for this is that decision trees categorize continuous variables which causes a loss of information (13). The decision tree also may have overestimated the risk of mortality in some subgroups but because our data was sparse in the highest risk deciles, it is difficult to determine from our data alone. However, a recent study found that logistic regression was less likely than a decision tree analysis to underestimate risk (14). This suggests that it is more probable that the decision tree overestimated risk.

5.4 Ontario Trauma Registry

The comprehensive data set of the OTR contains information for all trauma patients with an ISS greater than 12 and who were admitted to a lead trauma hospital or treated in the emergency department of a lead trauma hospital or who died in the emergency department of a lead trauma hospital after receiving treatment (15). The Ontario Trauma Registry is freely accessible and has a large number of patient records to analyze. Since it contains data on all trauma admissions for flail chest in Ontario, it is highly generalizable to all flail chest cases in Ontario. The OTR also has data for several patient characteristics that are measured objectively such as demographics, physiology, procedures, and mortality.

Using the OTR did have some limitations. Like other healthcare databases, it had some missing data for GCS that is unlikely to change. We attempted to account for this by using several models and examining if there were any differences (16). Another weakness of healthcare databases is that comorbidities are less likely to be correctly coded and are more likely to be missed (17). This is not surprising considering that this information is often not known at the time injury. This could have biased the risk estimate of number of comorbidities and mortality. Surgeons making use of the logistic regression scoring system should verify with the patient that their comorbidities have

been correctly recorded in full. Additionally, it was not possible to obtain cause of death information or to identify which patients underwent secondary operative repair of flail chest (i.e. patient undergoing surgery for a different system and surgeon decided to do operative repair of flail chest at the same time). Furthermore we were unable to distinguish bilateral flails from unilateral flail chests in the dataset which is unfortunate since we would expect bilateral flail chest patients to have worse outcomes and these have been previously estimated to be as common as or more common than unilateral flails (3). Also, we only had data on first recorded variables and we were not able to evaluate the effect of predictors over time in hospital. Finally, the OTR does not capture some relevant conditions well (such as shock and pulmonary contusion). Ideally, we would have preferred to identify hemorrhagic shock and spinal cord shock as well as characterize the extent of pulmonary contusion but these were not available in the OTR.

5.5 Role of risk scores in clinical practice

There are many risk scores available to identify at-risk subpopulations. Some of these models include logistic regression, artificial neural networks, decision trees, and hybrid techniques. For each model there are internal sources of variation. For example, logistic regression may be conducted using automated techniques (such as forward, backward, or stepwise selection with further variation in type of selection criteria employed) or the user can decide which terms should be included in the final model. There are different methods in decision tree analysis to identify the best partition in the data: Chi-squared Automatic Interaction Detection, Classification and Regression Tree, and boosting algorithms such as C5.0 (18). There is even variability in the method of validating the final model: cross validation, bootstrap sampling, and data-splitting (19).

This huge diversity in modeling makes ranking models difficult. Some studies have compared different modeling techniques and evaluated which models had the best discrimination. These studies are summarized in Appendix I. The measure of model discrimination was a c statistic for all the included studies. Four studies found that decision trees which employed boosting algorithms had the best discrimination (20-23). Three studies found that logistic regression models had the best discrimination; however,

the decision tree analyses included in some of the comparisons did not employ boosting algorithms (14, 18, 24). The ranking for neural networks varied between studies but was often in the middle or end of ranks (14, 18, 20-24). Hybrid techniques were not compared in the studies. The studies did not agree about the magnitude of the difference in c statistics between models (<5% difference, <10% difference, >20% difference) or if the models all reached the acceptable model discrimination of 0.80 (all model c statistics >0.80, all model c statistics <0.80) (14, 18, 20-24). Most studies did not address model calibration; however, one study found that a nomogram generated using logistic regression had fewer discrepancies from observed risk than a Classification and Regression Tree decision tree and an artificial neural network (14).

Does the literature indicate that some modeling techniques should be preferred for use in clinical practice over others? We would suggest that there is not enough evidence yet to suggest any one modeling technique is superior. Rather each model should be individually evaluated by its discrimination, calibration, relevancy and user-friendliness (14). For example, our results showed that logistic regression was more discriminate than a Classification and Regression Tree decision tree. However, the rules from a decision tree are easy and simple to apply whereas a calculator, app, or computer is needed when using the logistic regression model. The choice of which model to use is ultimately up to the discretion of the surgeon, however, in our humble opinion we prefer the logistic regression risk score because it makes use of more patient information, is more discriminate and may be less likely to overestimate risk in certain risk subgroups (14).

Applying the logistic regression risk score or decision tree risk score to clinical practice is not currently recommended because the models require prospective validation to determine their validity and user-friendliness (25). Additionally, because randomized trials have not yet shown evidence that operative repair of flail chest is a life-saving procedure, how to correctly interpret high risk scores is unclear (8-10). Definitive evidence is needed before a recommendation can be issued for how to proceed in high-risk for mortality cases however meta-analyses including non-randomized studies seem to suggest that these patients would benefit from operative repair as well (11-12). If it were determined that operative repair was a life-saving procedure, then patients with high risk

scores should be targeted for expedited operative repair. If it were determined that operative repair was not a life-saving procedure, then patients with lower risk scores would be considered ideal surgical repair candidates.

5.6 Implications for research

Previous randomized controlled trials included flail chest patients based on need for mechanical ventilation, number and location of rib fractures (≥ 6 , ≥ 3 fractured ribs with paradoxical movement, lower ribs only), no severe head injury (head AIS ≤ 3 , no “disturbed conscious level”, GCS ≥ 10), age (≥ 14 years, ≤ 80 years), without comorbidity, without spinal injury and without sepsis (1-3). Future studies evaluating the efficacy of operative repair of flail chest could use the logistic regression scoring system or the decision tree to identify high-risk for mortality cases that should be excluded as part of the study protocol. The scoring systems could also be used as a way to compare baseline characteristics in treatment groups: significant differences in average score would suggest inequality of group prognoses. At a minimum, the scoring systems show which risk factors are important for mortality and therefore should be controlled for when evaluating the efficacy of operative repair of flail chest. Two of the risk factors in the scoring systems had not already been found to be important: CPR and definitive airway (4, 8, 9, 11).

Stiell, the primary author of the Ottawa Ankle Rules, has suggested there are six stages in the formation of a mature clinical risk score: justification for the risk score, calculation of the model, prospective validation of the model and refining it as necessary, implementation of the risk score into clinical practice, determination of cost-effectiveness of the risk score, and the widespread dissemination and implementation of the risk score (25). According to this paradigm, the next step for our risk scores would be prospective validation. Future research could involve applying the risk scores in trauma centers throughout North America, recording outcome and evaluating their validity. Additionally, it would be possible to observe the number of operative repairs performed in hospital before and after implementing the risk scores and determining if the risk scores supported operative repair. Finally, satisfaction questionnaires to surgeons using the risk score

could be administered to determine if the risk scores were user-friendly or if improvements could be made.

5.7 Implications for clinical practice

The risk scores presented in our studies are still in the early stages of development and so they are not yet ready to be widely implemented (25). The main outcome the scoring systems address is mortality. The intent of the scoring systems is to allow surgeons to quantify individual risk of mortality to better identify candidates for operative repair. Patients who are at lower risk of mortality may not be good surgical candidates because they are healthy enough not to require it. Currently the indications for operative repair include failure to wean from ventilation, paradoxical movement of the chest wall during ventilation, persistent pain, progressive decline in pulmonary function, no severe pulmonary contusion, and no significant brain injury (27-28). Other candidates include patients with chest deformities too severe to heal on their own or patients who require thoracotomy for concomitant injuries (27). Since these indications are somewhat loosely defined, less experienced surgeons may benefit from the additional information these risk scores provide. Our hope is that when surgeons are equipped with better knowledge of patient risk, more flail chest patients can benefit from operative repair.

5.8 Conclusions

The risk scores we developed appear to be valid ways of calculating risk of in-hospital mortality in flail chest patients. They have the potential to be useful tools for surgeons considering operative repair of flail chest. Prospective validation of the risk scores is necessary before they can be widely implemented.

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Appendices

Appendix A: Randomized controlled trials evaluating efficacy of flail chest

Tanaka H et al. Surgical stabilization of internal pneumatic stabilization? a prospective randomized study of management of severe flail chest patients (17)			
<p>Patients or population: 37 flail chest patients included; patients were excluded if mechanical ventilation was not required, <6 ribs fractured, no acute respiratory failure, severe closed head or spinal injury (head AIS >3), age <14 years, history of heart, lung, kidney, or liver disease</p> <p>Settings: Kyorin University Hospital (Tokyo, Japan)</p> <p>Intervention: Surgical stabilization with Judet struts</p> <p>Comparison: Internal pneumatic stabilization</p>			
Outcomes	Without surgery	With surgery	p-value
Duration of mechanical ventilation	18.3 days	10.8 days	p<0.05
Duration of ICU stay	26.8 days	16.5 days	p<0.05
Rate of pneumonia	77%	24%	p<0.05
Granetzny A et al. Surgical versus conservative treatment of flail chest evaluation of the pulmonary status (18)			
<p>Patients or population: 40 flail chest patients with ≥ 3 fractured ribs with paradoxical movement included; patients were excluded if head trauma with disturbed conscious level, injuries that could be adversely affected by anesthesia, severe trauma to other systems, and fractures of upper three ribs only</p> <p>Settings: Cairo University clinic, Zagazing University clinic (Cairo, Egypt)</p> <p>Intervention: Surgical fixation using Kirschner wires</p> <p>Comparison: Adhesive plaster to the flail segment</p>			

Outcomes	Without surgery	With surgery	p-value
Duration of mechanical ventilation	12 days	2 days	p<0.001
Duration of ICU stay	14.6 days	9.6 days	p<0.001
Rate of pneumonia	50%	10%	p=0.014
Rate of mortality	15%	10%	p>0.05
Marasco SF et al. Prospective randomized controlled trial of operative rib fixation in traumatic flail chest (19)			
<p>Patients or population: 46 flail chest patients requiring mechanical ventilation with ≥ 3 consecutively ribs fractured in ≥ 2 places included; patients were excluded if age >80 years, spinal injuries, open rib fractures with soiling/infection, sepsis, GCS <10, and uncorrected coagulopathy</p> <p>Settings: The Alfred Hospital (Melbourne, Australia)</p> <p>Intervention: Inion resorbable plates, bicortical screws</p> <p>Comparison: Mechanical ventilator management</p>			
Outcomes	Without surgery	With surgery	p-value
Duration of mechanical ventilation	7.5 days	6.3 days	p=0.37
Duration of ICU stay	19 days	14 days	p=0.03
Rate of tracheostomy	70%	39%	p=0.04
Rate of pneumonia	74%	48%	p=0.07
Rate of mortality	4%	0%	p=0.87

Appendix B: Cohort studies evaluating markers of injury severity in thoracic trauma

Sirmali M et al. A comprehensive analysis of traumatic rib fractures: morbidity, mortality, and management (26)

Patients or population: 548 rib fracture patients (including 32 flail chest patients)

Settings: Ataturk Training and Research Hospital for Chest Disease and Chest Surgery (Ankara, Turkey)

Investigated markers of injury severity: Number of rib fractures, age, flail chest, gender

Findings: More complications observed with increasing number of rib fractures and increasing age

Freixinet J et al. Indicators of severity in chest trauma (27)

Patients or population: 1,772 chest trauma patients

Settings: Hospital Dr Negrín (Las Palmas, Spain)

Investigated markers of injury severity: RTS, age, extent of injury, number of rib fractures, lung contusion, hemothorax, shock, ventilation

Findings: Factors associated with mortality or complications include number of rib fractures ($p < 0.00001$), multiple injuries ($p < 0.05$), lung contusion ($p < 0.05$), ventilation ($p < 0.05$), shock ($p < 0.05$)

Perna V, Morera R. Prognostic factors in chest traumas: a prospective study of 500 patients (28)

Patients or population: 500 chest trauma patients (including 60 flail chest patients)

Settings: Asepeyo-Sant Cugat Hospital (Barcelona, Spain)

Investigated markers of injury severity: Degree of trauma, AIS, ISS, pre-hospital intubation, duration of ventilation, stay in ICU, number of rib fractures, pulmonary contusion, hemothorax, flail chest

Findings: Factors associated with mortality or complications include flail chest ($p < 0.00001$), number of rib fractures ($p < 0.00001$), age > 55 years ($p < 0.05$), pulmonary contusion ($p < 0.05$), ISS > 25 ($p < 0.05$)

Appendix C: Cohort studies evaluating mortality risk factors in flail chest

<p>Freedland M et al. The management of flail chest injury: factors affecting outcome (29)</p>
<p>Patients or population: 57 flail chest patients</p> <p>Settings: Detroit Receiving Hospital (Detroit, United States)</p> <p>Investigated mortality risk factors: Injury etiology, age, bilateral flail, pulmonary contusion, hemo/pneumothorax, ISS, shock, blood transfusion, ventilation</p> <p>Findings: Factors associated with mortality include ISS ≥ 31 ($p < 0.05$), bilateral flail ($p < 0.005$), blood transfusion ($p < 0.001$), age ≥ 50 years ($p < 0.05$)</p>
<p>Athanassiadi K et al. Management of 150 flail chest injuries: analysis of risk factors affecting outcome (30)</p>
<p>Patients or population: 150 flail chest patients</p> <p>Settings: General Hospital of Nikea-Piraeus (Athens, Greece)</p> <p>Investigated mortality risk factors: Age, comorbidities, hemo/pneumothorax, ISS, ventilation</p> <p>Findings: No evidence of any mortality risk factors ($p > 0.05$)</p>

Appendix D: Cohort and case-control studies evaluating mortality risk factors in thoracic trauma

Bulger EM et al. Rib fractures in the elderly (31)

Patients or population: 464 rib fracture patients

Settings: Harborview Medical Center (Seattle, United States)

Investigated mortality risk factors: Pulmonary complications, duration of ventilation, analgesic technique, AIS in chest region

Findings: Factors associated with mortality include number of rib fractures (OR for each additional rib fracture=1.19, $p<0.001$), age ≥ 65 years (OR 2.50, $p<0.001$)

Flagel BT et al. Half-a-dozen ribs: the breakpoint for mortality (32)

Patients or population: 64,661 rib fracture patients

Settings: National Trauma Data Bank (United States)

Investigated mortality risk factors: Number of rib fractures, ISS, pneumonia, acute respiratory distress syndrome, pulmonary embolus, pneumothorax, empyema, AIS, ventilation, duration of ventilation, epidural analgesia

Findings: Factors associated with mortality include number of rib fractures ($p<0.02$)

Wang SH et al. Prognostic analysis of patients with blunt chest trauma admitted to an intensive care unit (33)

Patients or population: 127 adult chest trauma patients (intrathoracic injuries with hemothorax, pneumothorax, flail chest or acute respiratory insufficiency and associated extrathoracic injuries including head trauma, internal bleeding and pelvic or extremity fractures)

Settings: Changhua Christian Hospital (Changhua, Taiwan)

Investigated mortality risk factors: APACHE II, GCS, Therapeutic Intervention Scoring System (TISS), ISS, PaO₂/FIO₂ ratio, shock

Findings: Factors associated with mortality include APACHE II (mean 19 points in non-survivors vs. mean 12 points in survivors, p=0.002), TISS (mean 39 points in non-survivors vs. mean 29 points in survivors, p=0.019), GCS (mean 8 points in non-survivors, mean 14 points in survivors, p<0.001), decreased PaO₂/FIO₂ ratio (mean 211 in non-survivors, mean 340 in survivors p=0.002), shock (93% in non-survivors, 42% in survivors, p<0.001)

Lien YC et al. Risk factors for 24-hour mortality after traumatic rib fractures owing to motor vehicle accidents: a nationwide population-based study (34)

Patients or population: 18,856 rib fracture patients (caused by traffic collisions, first-time admissions)
Settings: National Health Insurance Research Database (Taiwan)

Investigated mortality risk factors: Sex, age, ≥ 6 rib fractures, hemo/pneumothorax, extremity fracture, pelvic fracture, vertebral column fracture, sternum fracture, scapula fracture, aortic rupture, head injury, spleen injury, liver injury, heart injury, diaphragm injury, hospital characteristics, flail chest

Findings: Factors associated with mortality include ≥ 6 rib fractures (OR 3.16, p<0.001), hemo/pneumothorax (OR 3.15, p<0.001), head injury (OR 4.29, p<0.001), spleen injury (OR 1.83 p<0.05), liver injury (OR 4.39, p<0.001), heart injury (OR 4.48, p<0.001), diaphragm injury (OR 3.16, p<0.05) extremity fracture (OR 1.74, p<0.001), pelvic fracture (OR 2.92, p<0.001), age ≥ 74 years (OR 3.29, p<0.001)

Appendix E: Meta-analysis of studies evaluating mortality risk factors in thoracic trauma

Battle CE et al. Risk factors that predict mortality in patients with blunt chest wall trauma: a systematic

review and meta-analysis (35)

Studies: 29 English and non-English articles evaluating mortality risk factors in blunt chest wall trauma patients (EMBASE, MEDLINE, Cochrane Library, Emergency Medicine conference abstracts)

Investigated mortality risk factors: Vital capacity, age, number of rib fractures, pre-morbid conditions, pneumonia

Findings: Factors associated with mortality include age ≥ 65 years (OR 1.98, $p < 0.00001$), ≥ 3 rib fractures (OR 2.02, $p < 0.00001$), ≥ 1 pre-morbid conditions (OR 2.43, $p = 0.04$), pneumonia (OR 5.24, $p < 0.00001$)

Appendix F: Validation study of scoring systems as predictors of mortality in thoracic trauma

Esme H et al. The prognostic importance of trauma scoring systems for blunt thoracic trauma (36)

Patients or population: 152 blunt thoracic trauma patients

Settings: Afyon Kocatepe University (Afyon, Turkey)

Investigated scoring systems: RTS, TRISS, ISS, Lung Injury Scale, Chest Wall Injury Scale

Findings: TRISS was the only scoring system found to predict mortality

Appendix G: List of the 9 lead trauma hospitals and geographical location in Ontario

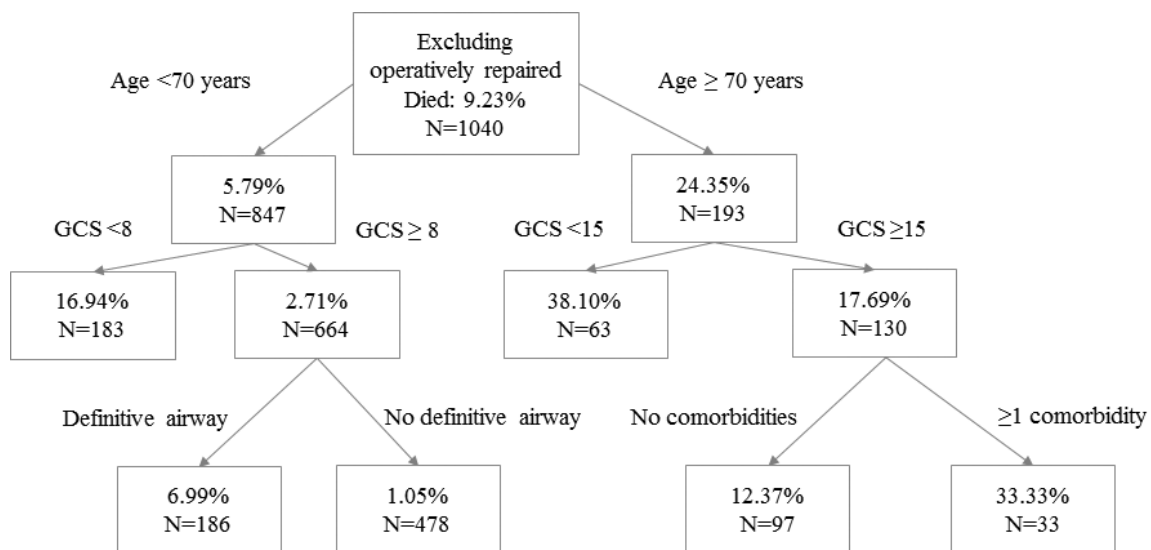
Facility	City
Thunder Bay Regional Hospital	Thunder Bay
St. Michael's Hospital	Toronto
London Health Sciences Centre	London
The Ottawa Hospital	Ottawa
Hamilton Health Sciences Corporation	Hamilton
Kingston General Hospital	Kingston
Hotel Dieu-Grace Hospital	Windsor
Sunnybrook Health Sciences Centre	Toronto
Sudbury Regional Hospital	Sudbury

Appendix H: Excel formulas* for logistic regression scoring calculator

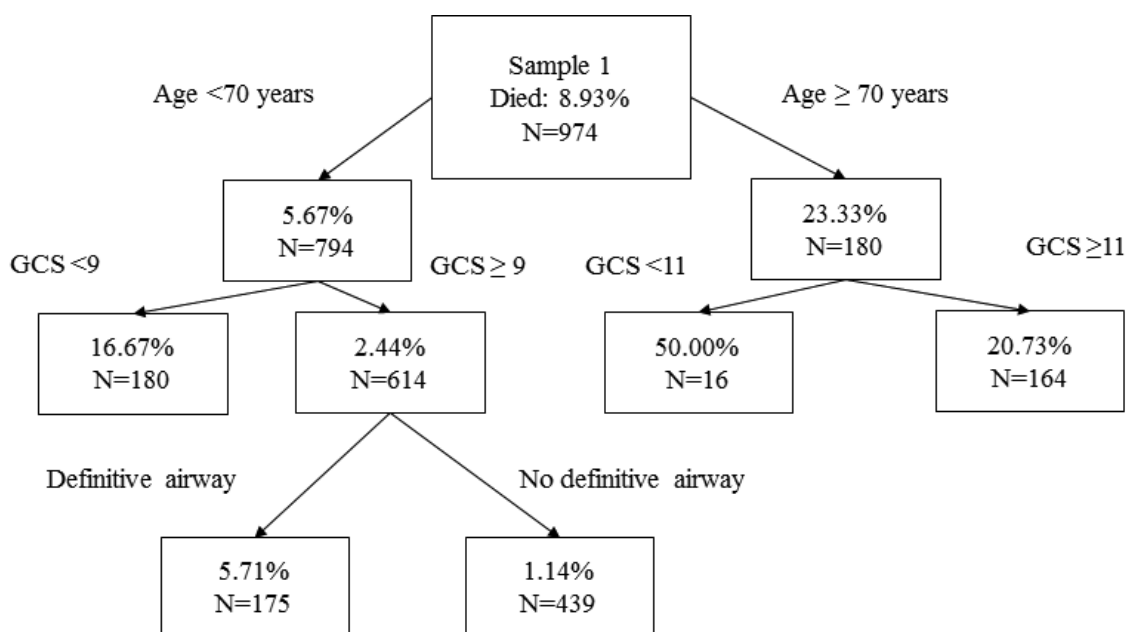
	Excel formula
Age	=IF(B2<30,0,((ROUNDDOWN((B2/10),0)-2)*2))
GCS	=IF(B3="",0,ROUNDDOWN((15-B3)/2,0))
Definitive airway	=IF(B4="Y",2,0)
Ventilation	=IF(B5="Y",1,0)
Number of comorbidities	=B7
CPR	=IF(B6="Y",2,0)

*Where the B2, B3, B4, B5, B6 and B7 cells are where the surgeon would enter the patient characteristic value. The cells containing the formulas would then be summed to give a summary risk score.

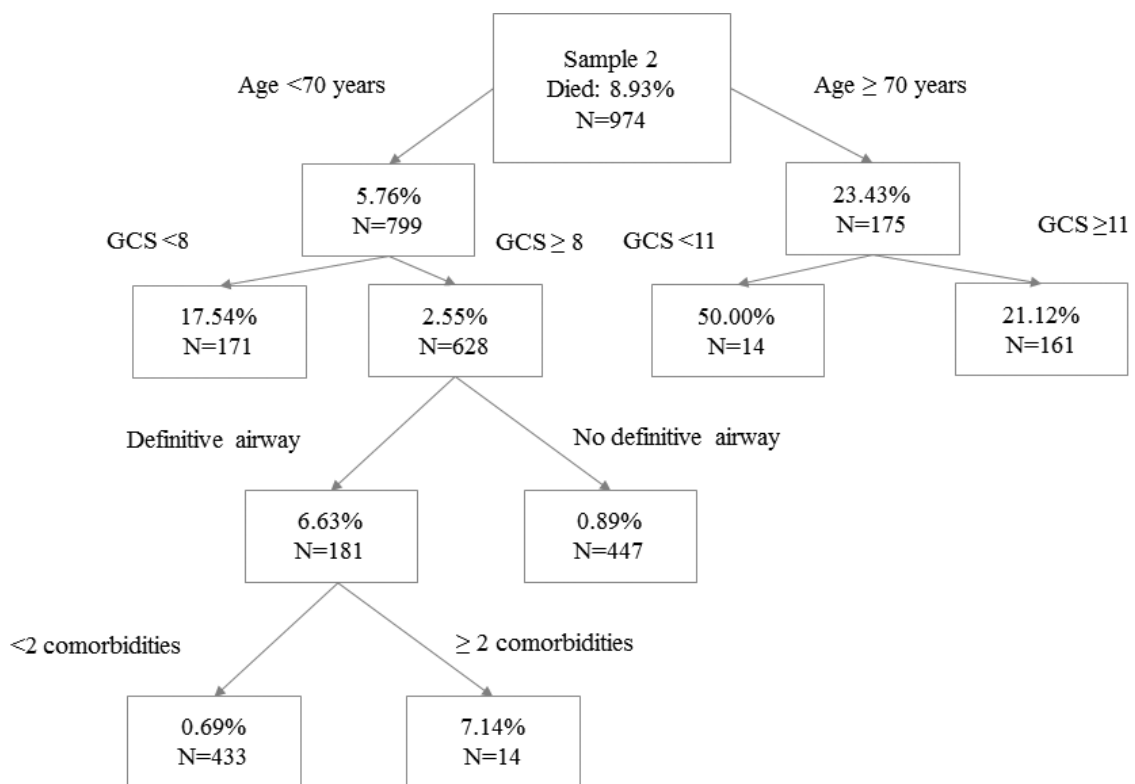
Appendix I: Decision trees



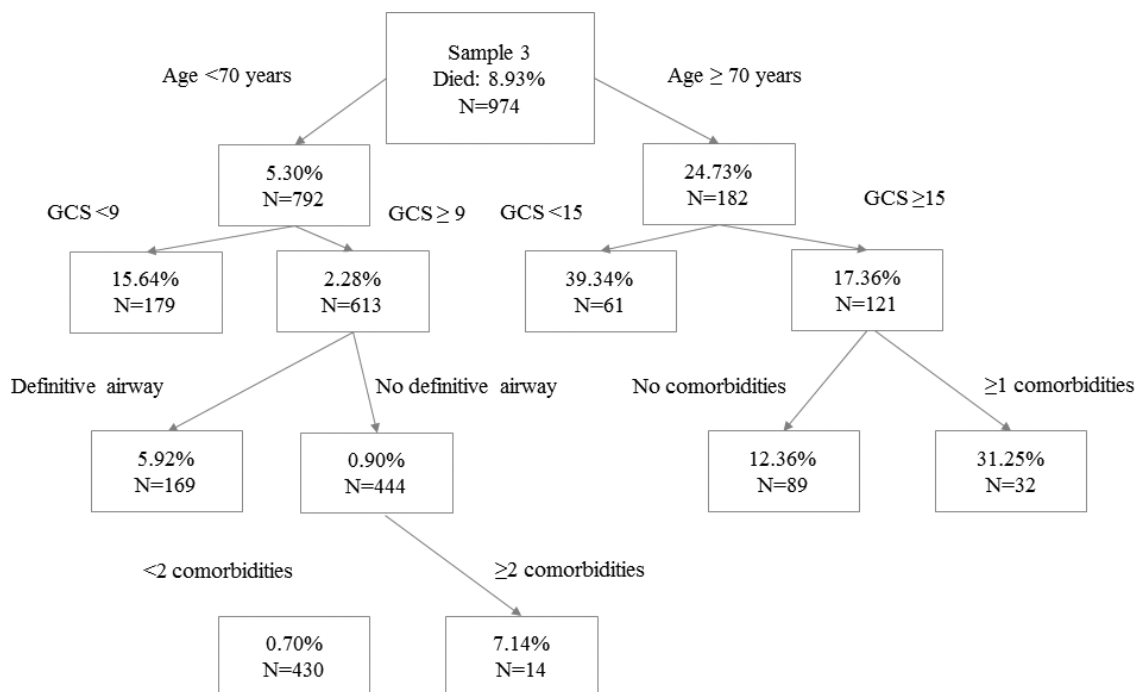
Decision tree excluding operatively repaired patients



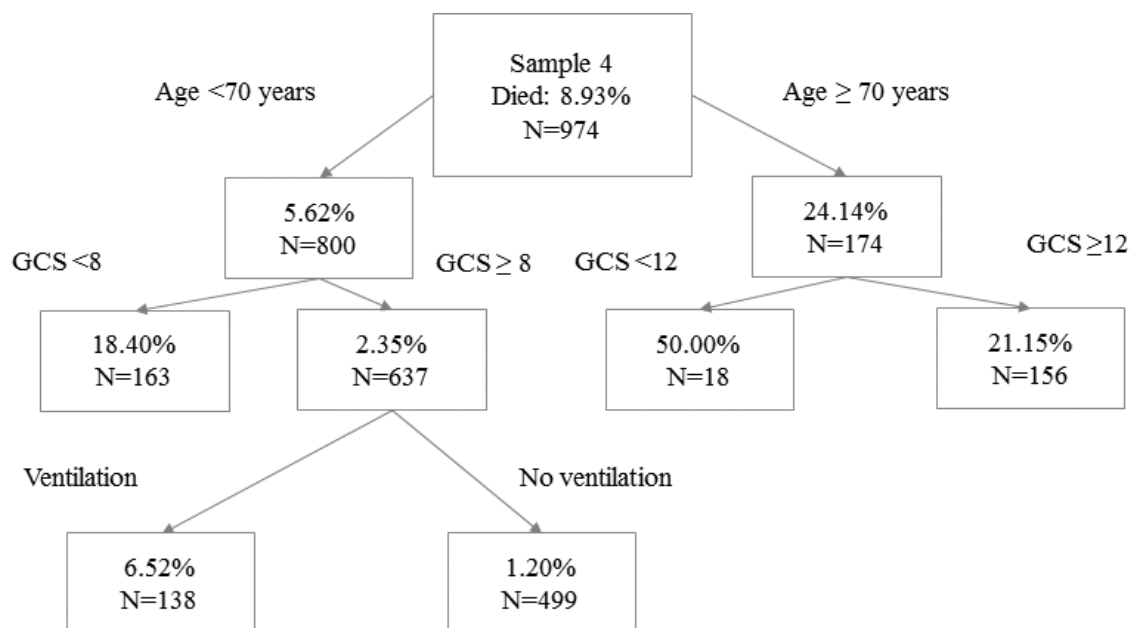
Decision tree of subsample 1



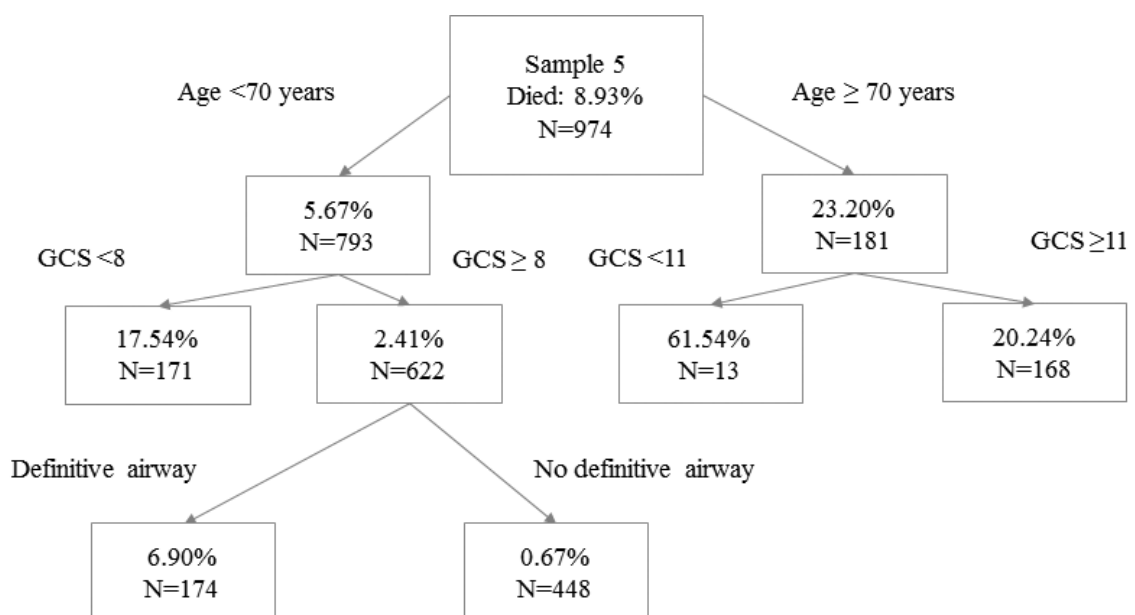
Decision tree of subsample 2



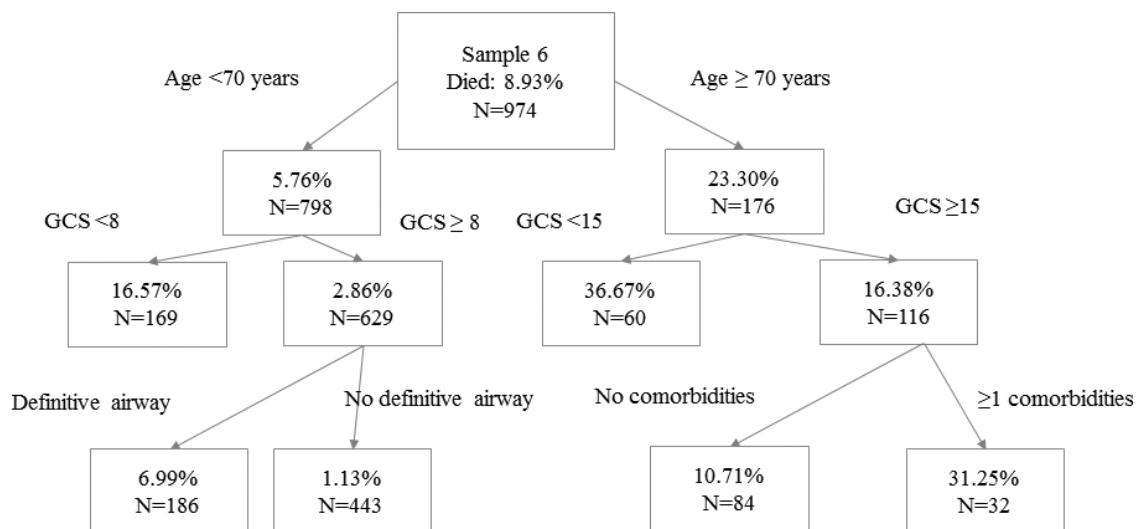
Decision tree of subsample 3



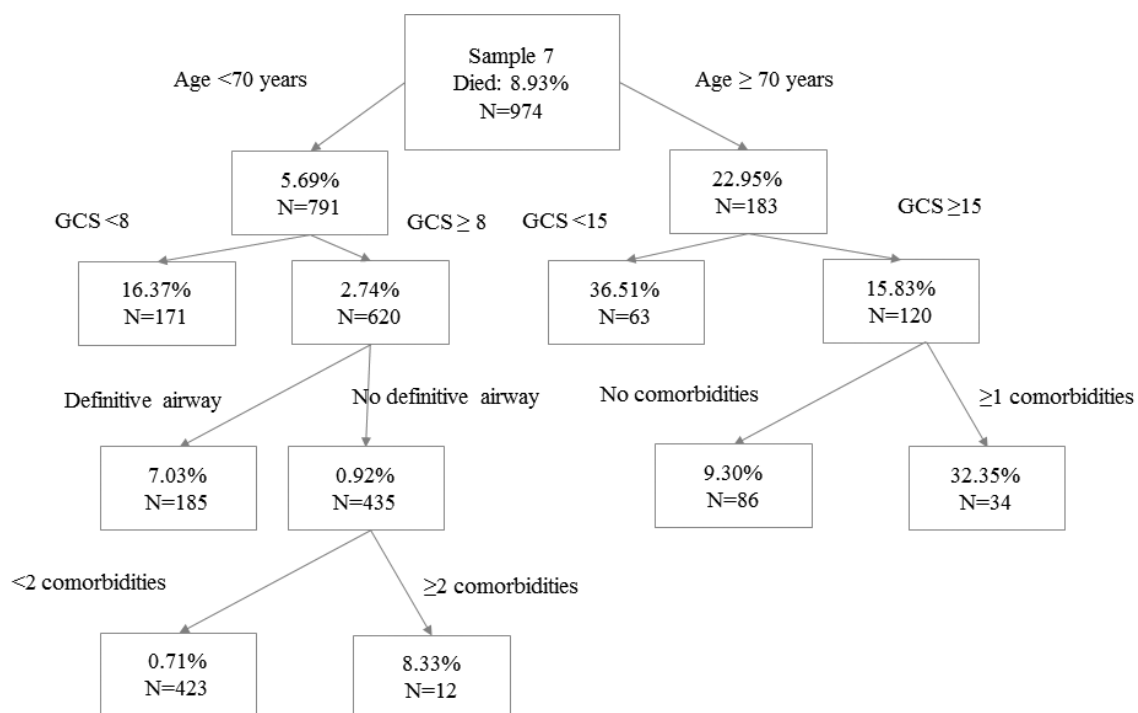
Decision tree of subsample 4



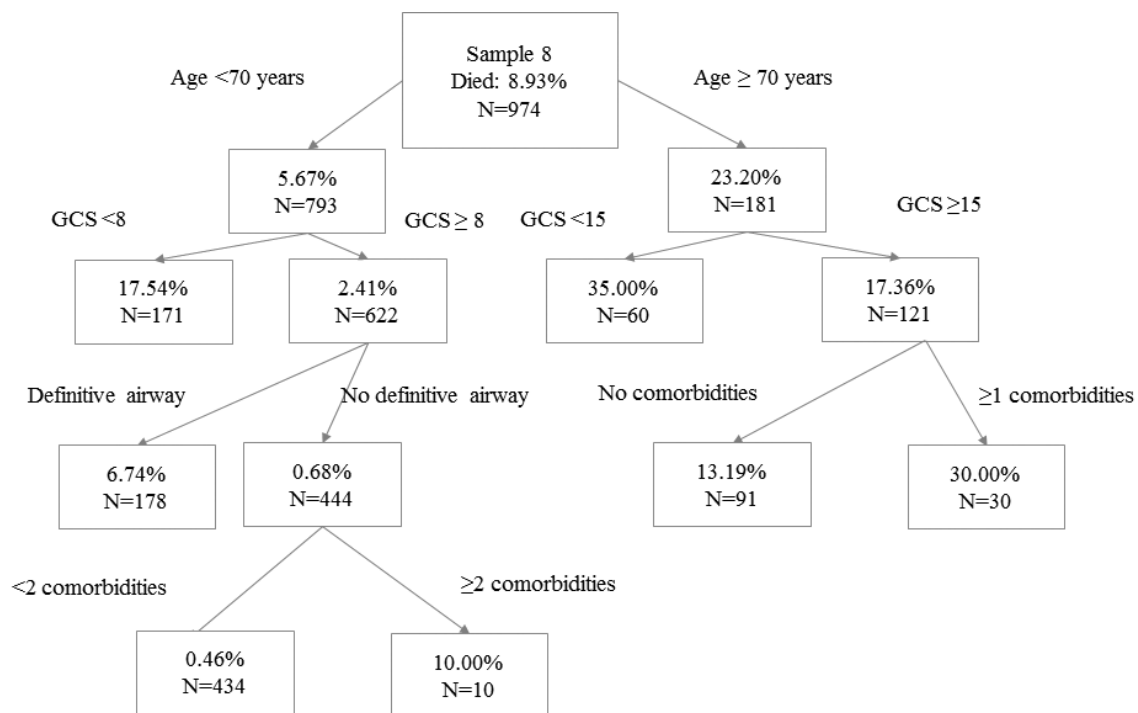
Decision tree of subsample 5



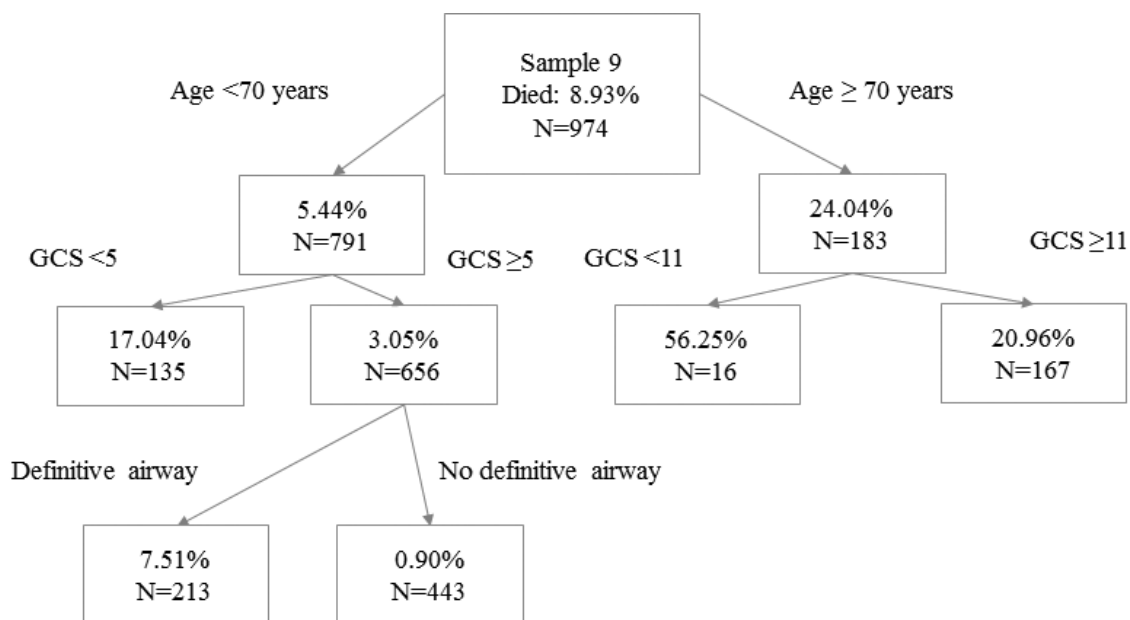
Decision tree of subsample 6



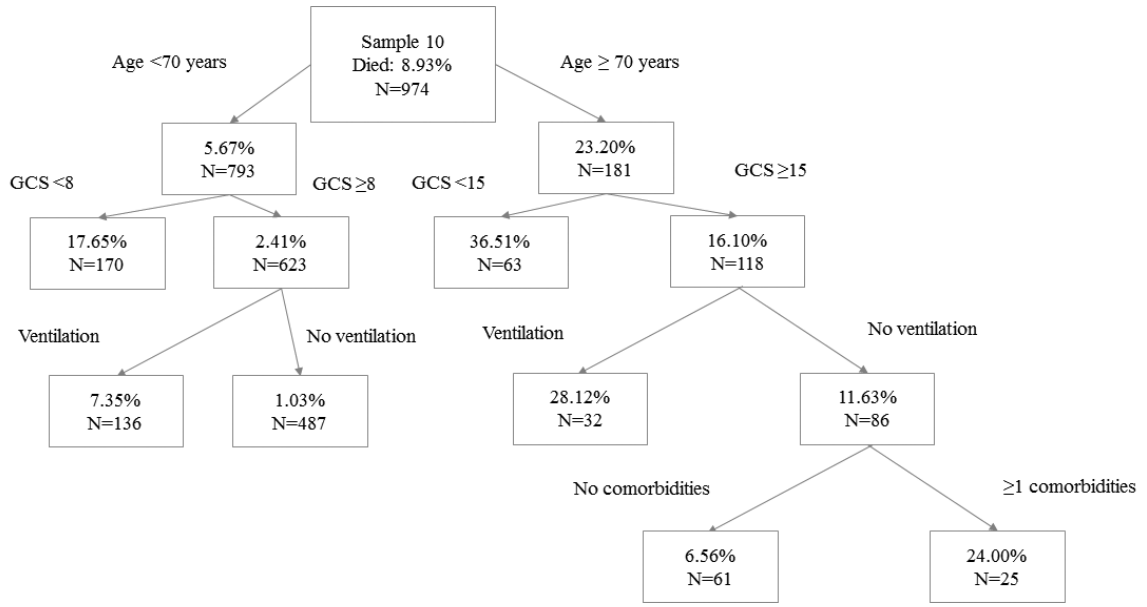
Decision tree of subsample 7



Decision tree of subsample 8



Decision tree of subsample 9



Decision tree of subsample 10

Appendix J: Studies ranking predictive modeling techniques

Kim S et al. A Comparison of Intensive Care Unit Mortality Prediction Models through the Use of Data Mining Techniques (20)	
<p>Patients or population: 38,474 ICU admissions</p> <p>Settings: University of Kentucky Hospital from January 1998 to September 2007 (Lexington, United States)</p> <p>Investigated modeling techniques: decision tree using C5.0 algorithm, forward logistic regression, artificial neural network back-propagation with two hidden layers</p> <p>Findings:</p>	
Modeling technique	C-statistic
Decision tree	0.892
Logistic regression	0.871
Artificial neural network	0.874
Chun FK et al. Critical appraisal of logistic regression-based nomograms, artificial neural networks, classification and regression-tree models, look-up tables and risk-group stratification models for prostate cancer (14)	
<p>Patients or population: 2,982 patients for decision tree comparison with logistic regression, 3,980 for artificial neural network comparison with logistic regression</p> <p>Settings: Not stated</p> <p>Investigated modeling techniques: logistic regression, Classification and Regression Tree decision tree, artificial neural network</p> <p>Findings: Logistic regression was significantly more accurate than the decision tree and artificial neural network ($p < 0.001$) and was less likely to underestimate risk</p>	

Delen D et al. Predicting breast cancer survivability: a comparison of three data mining methods (21)

Patients or population: 202,932 breast cancer patients in SEER database from 1973 to 2000

Settings: Ataturk Training and Research Hospital for Chest Disease and Chest Surgery (Ankara, Turkey)

Investigated modeling techniques: logistic regression, C5.0 decision tree, multi-layer artificial neural network with back-propagation

Findings:

Modeling technique	Mean C-statistic
Decision tree	0.936
Logistic regression	0.892
Artificial neural network	0.912

Gortzis LG et al. Predicting ICU survival: a meta-level approach (22)

Patients or population: 204 ICU admissions

Settings: Tertiary care teaching hospital (Greece) from August 2003 to December 2005

Investigated modeling techniques: logistic regression, decision tree, artificial neural network with one hidden layer

Findings:

Modeling technique	C-statistic
Decision tree	0.877
Logistic regression	0.820
Artificial neural network	0.806

Sugimoto M et al. Comparison of robustness against missing values of alternative decision tree and multiple logistic regression for predicting clinical data in primary breast cancer (23)

Patients or population: Models trained on 150 patients, models validated on 173 patients

Settings: Tokyo Metropolitan Cancer and Infectious Diseases Center, Osaka National Hospital, Tsukuba University Hospital, Niigata Cancer Center Hospital, National Kyushu Cancer Center, Aichi Cancer Center (Osaka, Japan)

Investigated modeling techniques: logistic regression, C5.0 decision tree with ensemble methods

Findings: Decision tree had a significantly higher performance than logistic regression (C statistic of 0.78 vs. 0.77, $p < 0.0001$)

Van der Ploeg T et al. Prediction of intracranial findings on CT-scans by alternative modelling techniques (18)

Patients or population: 3181 patients with minor head injury from CT in Head Injury Patients database

Settings: Not stated

Investigated modeling techniques: Bayes network, multi-layer artificial neural network, Chi-squared Automatic Interaction Detection decision tree, Classification and Regression Tree decision tree, logistic regression

Findings:

Modeling technique	Optimism-corrected C-statistic
Artificial neural network	0.744
Chi-squared Automatic Interaction Detection decision tree	0.684
Classification and Regression Tree decision tree	0.549
Logistic regression	0.783

Terrin N et al. External validity of predictive models: a comparison of logistic regression, classification trees, and neural networks (24)

Patients or population: Simulated sample of 50,000

Settings: Not applicable

Investigated modeling techniques: Forward stepwise logistic regression, decision tree, artificial neural network with one hidden layer

Findings:

Modeling technique	C-statistic
Logistic regression	0.741
Decision tree	0.682
Artificial neural network	0.724

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