A Clinical Prediction Model for the Early Identification of the Need for Major Intervention in Patients with Traumatic Hemorrhage

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Table of Contents

Thesis Abstract

Background: There is a lack of well-validated clinical decision tools to assist clinicians with risk stratification of bleeding trauma patients.

Objective: This thesis derives and validates a clinical prediction score in order to identify patients requiring major interventions for traumatic hemorrhage.

Methods: We created a model based on the pre-specification of predictors. We conducted a systematic review of prediction models and a survey of traumatologists to identify candidate predictors. We conducted a derivation study of 748 trauma patients from 2014 to 2017.

Results: The final model included systolic BP, clinical exam, lactate, FAST and CT. The c-statistic was 0.953 (naïve) and 0.952 following optimism-correction with bootstrap validation.

Discussion: This thesis utilizes pre-specification to minimize reliance on small datasets and potential for over-optimism. Pre-specification is based on the best available knowledge within the literature and clinical expert community.

Conclusion: A simple score is proposed for risk stratification of bleeding trauma patients.

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Author's Contributions

Manuscript #1: "Early identification of patients requiring massive transfusion, embolization or hemostatic surgery for traumatic hemorrhage: a systematic review protocol"

Authors Contributions: AT, CV and MT contributed to study conception. AT, CV, MT, MM, JL, ES contributed to study design. AT drafted the manuscript which was revised by all authors.

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Authors Contributions: AT, CV and MT contributed to the study design and conception. AT, MM completed screening and data extraction. AT conducted the statistical analysis. AT, CV,

MT, MM, JL, ES contributed to data interpretation. AT drafted the manuscript which was revised by all authors.

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Authors Contributions: AT, CV, MT, MM, JL contributed to the study design and conception. AT, MM, JL contributed to survey design and piloting. AT conducted the statistical analysis. AT, CV, MT, MM, JL contributed to data interpretation. AT drafted the manuscript which was revised by all authors.

Manuscript #4: Early identification of the need for major intervention in patients with traumatic hemorrhage: development and internal validation of the Canadian Bleeding (CAN-BLEED) score

Authors Contributions: AT, CV, MT, MM, JL contributed to the study design and conception. AT completed data extraction. AT conducted the statistical analysis under MT's supervision. AT, CV, MT, MM, JL, ES contributed to data interpretation. AT drafted the manuscript which was critically revised by all authors.

Required Ethics Approvals

Manuscript #1: "Early identification of patients requiring massive transfusion, embolization or hemostatic surgery for traumatic hemorrhage: a systematic review protocol"

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Required Approval: Ethics approval was received on March 20th, 2017 following review by the Ottawa Health Science Network Research Ethics Board (OHSN-REB).

Manuscript #4: A derivation and internal validation study for a clinical prediction model for the early identification of the need for major intervention in patients with traumatic hemorrhage

Required Approval: Ethics approval was received on March 20th, 2017 following review by the Ottawa Health Science Network Research Ethics Board (OHSN-REB).

Glossary

AIC – Akaike Information Criterion

ATLS – Advanced Trauma Life Support

BE – Base Excess

BP – Blood Pressure

CBC – Complete Blood Count

CHARMS – Critical Appraisal and Data Extraction for Systematic Reviews of Modeling Studies

CI – Confidence Interval

CT – Computed Tomography

ED – Emergency Department

EMB – Embolization

FAST – Focussed Abdominal Sonography for Trauma

GCS – Glasgow Coma Scale

HGB – Hemoglobin

HCT – Hematocrit

INR – International Normalized Ratio

ISS – Injury Severity Score

mmHg – Millimeters of Mercury

MT – Massive Transfusion

PROGRESS – Prognosis Research Strategy

PROSPERO – International Prospective Register of Systematic Reviews

SURG – Surgery

ROC – Receiver Operating Curve

Chapter 1 – Introduction

This chapter outlines the thesis objectives and overview of included manuscripts.

1.1 Research Program Objective

Primary Objective

The primary objective of this research program and thesis is to improve the process of risk stratifying bleeding trauma patients, reduce the time to intervention and ultimately reduce the morbidity and mortality associated with major traumatic hemorrhage. Specifically, in this thesis work we sought to:

1. Systematically review the literature in order to identify candidate predictors from high quality studies.
2. Survey Canadian traumatologists in order to identify candidate predictors of high clinical importance.
3. Derive and internally validate a clinical prediction model for the early identification of patients requiring major intervention for traumatic hemorrhage, utilizing the findings of the systematic review and survey to inform predictor selection.

   In order to for this decision tool to be well developed, accurate and adopted, we strived to achieve the following qualities:

1. The clinical prediction model will incorporate clinical, laboratory or imaging findings available to any major trauma centre within the first hour of initial assessment and resuscitation.
2. The clinical prediction model will adhere to the highest standard of methodological quality as outlined by the Prognosis Research Strategy guidelines. The model will

incorporate variable pre-specification based on the best available clinical expertise and existing literature.

3. The clinical prediction model will balance clinical and methodological priorities and aim to embrace practicality and functionality for clinical application.

1.2 Overview of Thesis and Included Manuscripts

Chapter 2 – Background

This chapter outlines the current deficiencies in the assessment of traumatic hemorrhage. We present the consequences of blood loss, discuss the challenges of identifying the source and extent of bleeding, review the clinical tools available to traumatologists to guide bedside decision making and demonstrate the need for an evidence-based approach to assessment as well as the management options. Lastly, we discuss the methodology for developing a high quality clinical prediction model.

Chapter 3 – Systematic Review Meta-Analysis of Clinical Prediction Models

This chapter summarizes and describes the existing clinical prediction modeling literature for predicting need for intervention in traumatic hemorrhage. We conduct a systematic review and meta-analysis in order to identify candidate predictors to inform the pre-specification of the clinical prediction model. We incorporate the protocol manuscript “Early identification of patients requiring massive transfusion, embolization or hemostatic surgery for traumatic hemorrhage: a systematic review protocol” and the review manuscript “A systematic review and meta-analysis of clinical prediction models for the early identification of the need for major intervention in traumatic hemorrhage”.

Publication: Tran A, Matar M, Steyerberg EW, Lampron J, Taljaard M, Vaillancourt C. Early identification of patients requiring massive transfusion, embolization or hemostatic surgery for traumatic hemorrhage: a systematic review protocol. Systematic Reviews, 2017 April. https://doi.org/10.1186/s13643-017-0480-0

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Chapter 4 – National Survey of Canadian Traumatologists

This chapter describes Canadian trauma community's valuation of predictors for the assessment of traumatic hemorrhage. We conducted a national survey of Canadian traumatologists to create a clinical expert ranking of predictors to inform the pre-specification of the clinical prediction model. We incorporate the manuscript "A national survey of Canadian traumatologists' valuation of predictors for the identification of clinically significant bleeding in trauma patients".

Chapter 5 – Clinical Prediction Model Derivation & Internal Validation

This chapter describes the development and internal validation of the Canadian Bleeding Score. We incorporate the manuscript "A derivation and internal validation study for a clinical prediction model for the early identification of the need for major intervention in patients with traumatic hemorrhage".

Chapter 6 – Thesis Summary

This chapter provides a summary of the thesis and key findings and outlines the next steps for future research.

Chapter 2 – Background

This chapter reviews important concepts in traumatic hemorrhage assessment and management, including the Advanced Trauma Life Support protocol and other diagnostic aids available to the clinician. The difficulties of appropriate risk stratification of bleeding trauma patients are discussed and the concept of clinical prediction modeling is introduced.

2.1 Importance of Identifying Hemorrhage

Hemorrhage is a major cause of early mortality following a traumatic injury [1] and is the most common cause of preventable death among civilian and military trauma [2]. The progression and consequences of significant blood loss occur quickly as death from hemorrhagic shock or exsanguination often occurs within the first six to twelve hours [3]. In fact, it is responsible for the majority of deaths in the operating room and nearly half of all deaths within the first 24 hours following an injury [4]. The resuscitation of these patients is further complicated by the physiologic consequences of a major traumatic injury, which include the classic "triad of death" that is hypothermia, acidosis and coagulopathy [5]. These physiologic interactions compound over time and result in an accelerated bleeding state which, when not lethal, can also lead to considerable morbidity and mortality. Significant blood loss leads to a state of global hypoperfusion, termed hemorrhagic shock, resulting in oxygenation starvation and end-organ dysfunction [6]. The presence of hemorrhagic shock is a known prognostic marker of poor outcome and the amount of blood loss is directly tied to increased resuscitation requirements, more pronounced physiologic derangements and increased risk of death [7]. Ongoing bleeding that is not quickly identified or well controlled may necessitate the urgent intraoperative sacrifice of organs or limbs. The late consequences of hemorrhagic shock relate to the physiologic insult suffered during the prolonged state of oxygen deprivation, most notably long-term organ failure and increased susceptibility to infection. The early recognition of

hemorrhage therefore greatly influences the potential for aggressive, effective therapeutic interventions in order to improve outcomes and reduce mortality [1].

2.2 Challenges of Identifying Hemorrhage

While some patients present to hospital with obvious visual evidence of bleeding and physiologic abnormality, there is a large proportion of the trauma population for whom these findings are not readily apparent. For a typical 70 kg male patient, the expected total body blood volume is 7% or approximately 5 litres. However, traumatic injuries have the potential for significant internal blood loss with several litres hidden within the thoracic, abdominal, pelvic and long bone compartments. In a study of preventable deaths from hemorrhage at a Canadian level 1 trauma centre (highest standard for trauma centre designation), up to one in six deaths were judged to have been preventable and caused by significant delays in identifying the major source of bleeding [8]. For patients presenting with penetrating abdominal trauma and hemorrhagic shock, centres with higher annual trauma volumes were shown to have significantly lower rates of mortality, hypothesized to be related to clinician experience as well as the systems in place to recognize and manage serious injury [9].

2.3 Management of Significant Hemorrhage

Beginning with the prehospital encounter of the bleeding trauma patients, every effort should be made to minimize the time between the injury and the initial resuscitation [10]. The mainstay of treatment involves early identification of patients at risk for hemorrhagic shock in order to provide blood products and control of the bleeding source if necessary [11]. In many cases, this blood loss necessitates significant blood transfusion volumes. Approximately 10% of trauma patients will require at least one blood transfusion while up to a third of patients will

require a massive transfusion (commonly defined as ten or more units of blood) within the first 24 hours [11]. However, the timely provision of blood products can face hurdles related to time and resource limitations [12]. Therefore, massive transfusion protocols have been developed in order to provide efficient, systematic pathways for activation in order to decrease time to blood product availability, reduction in delivery times, as well as reduction in blood product waste. While the timely delivery of large volumes of blood may be necessary for restoration of adequate perfusion, there is an independent association between massive transfusion and the development of multi-organ failure and late mortality, believed to be related to an immune-modulatory effect that predisposes patients to infection. Therefore, when possible, efforts should be made to rapidly control the bleeding source as opposed to simply replacing the losses [10]. These options include angioembolization, a specialized procedure for endovascular hemostasis, or urgent surgery for hemostasis. Embolization is offered for single vessel injuries amenable to hemostasis by minimally invasive techniques in patients with stable hemodynamics. Surgical hemostasis may involve exploration of the thoracic, abdominal or pelvic cavities to repair vascular injuries or provide tamponade for solid organ injuries and is considered the intervention of choice for hemodynamically unstable patients. Regardless, the clinician's priority during the initial resuscitation is to provide initial stabilization and quickly determine which patients will require an escalation of care to activate the necessary pathways for massive transfusion, embolization or surgery. The clinician's ability to quickly and efficiently risk stratify their bleeding patients early into the initial assessment is paramount in determining that patient's eventual outcome.

2.4 Advanced Trauma Life Support Protocol and Other Clinical Decision Aids

In an effort to standardize and improve an approach to trauma assessment, the American College of Surgeons Committee on Trauma has worked to establish and update the Advanced

Trauma Life Support (ATLS) algorithm for the initial care and management of the injured patient [13]. Since its inception in the 1970s, the ATLS course has been taught to over a million physicians in 63 countries worldwide.

Table 1 – ATLS Classification of Hemorrhagic Shock (70 kg male example)

Class of Hemorrhage	I	II	III	IV
Blood Loss (mL)	< 750	750 – 1500	1500 – 2000	> 2000
Blood Loss (% Blood Volume)	<15%	15-30%	30-40%	>40%
Heart Rate	< 100	100 – 120	120 – 140	> 140
Systolic BP	Normal	Normal	Decreased	Decreased
Pulse Pressure	Normal or Increased	Decreased	Decreased	Decreased
Respiratory Rate	14 – 20	20 – 30	30 – 40	> 35
Urine Output (mL/hr)	> 30	20 – 30	5 – 15	Negligible
CNS/mental status	Slightly anxious	Mildly anxious	Anxious, confused	Confused, lethargic
Initial Fluid Replacement	Crystalloid	Crystalloid	Crystalloid and blood	Crystalloid and blood

Adapted from Advanced Trauma Life Support Guidelines 9th Edition [13]

With regards to traumatic bleeding, these guidelines classify hemorrhage shock into four distinct classes of severity based on assessment of vital signs, presented in Table 1, with proposed thresholds for intervention with crystalloid fluids or blood products. For patients with presumed modest blood loss, crystalloid fluids such as Ringer's Lactate or normal saline are provided to offset the lost volume and improve circulation. For patients with more significant blood volume deficits, blood products in the form of packed red cells, are provided instead due to their additional benefit of improving oxygen carrying capacity and delivery. Presumably, patients with significant blood volume losses and poor end organ perfusion would declare themselves accordingly with obvious disturbances in heart rate and systolic blood pressure. However, these concepts have come under greater scrutiny and criticism in recent years. A large

database validation using the Trauma Audit and Research Network in the United Kingdom demonstrated that the ATLS algorithm overestimates the degree of tachycardia and hypotension associated with increasing blood loss [14]. In other words, patients may lose a significant amount of blood before profound changes in heart rate or blood pressure are observed. Similarly, another multi-centre database validation using the Trauma Registry of the German Society for Trauma Surgery found that less than 10% of patients could be classified according to the ATLS protocol [15]. The remaining patients demonstrated conflicting clinical parameters that would not permit for classification into any ATLS class of hemorrhage. It is not surprising then to consider that in a 2012 international survey of ATLS course directors and instructors, only 10.9% of respondents stated that they considered the ATLS classification of hemorrhagic shock to be a "good guide for fluid resuscitation and blood product transfusion" [16].

Unfortunately, there exist only few commonly used alternatives to the ATLS classification for guiding bedside clinical decision making in traumatic hemorrhage. The European Guidelines for the Management of Traumatic Bleeding summarize the existing literature and provide evidence-based recommendations but not in a form easily accessible and applicable to clinicians at the bedside [10]. The guidelines recommend that the clinician base the assessment on a "combination of patient physiology, anatomical injury pattern, mechanism of injury and the patient's response to initial resuscitation". In addition, it is recommended that clinicians also consider the findings of initial laboratory tests and early imaging such as FAST ultrasound or CT imaging.

Given the volume and variety of available predictors, there has recently been considerable interest in clinical prediction modeling research for traumatic hemorrhage with 54 such studies having been published since 2010 [17]. Much of the work conducted in the domain

of clinical decision aids or scores for assessment of traumatic hemorrhage focusses primarily on the prediction of massive transfusion as a surrogate for clinically significant bleeding. These include the ABC score [18], the Trauma Associated Severe Hemorrhage (TASH) score and the McLaughlin score [1], presented in Table 2. However, the utilization of massive transfusion as

Table 2 – Existing Massive Transfusion Prediction Scores

Massive Transfusion Prediction Score	Score Composition
TASH Score [Yucel 2006]	Sex Hemoglobin Base Excess Systolic BP Heart Rate FAST ultrasound Clinically Unstable Pelvis Open or Dislocated Femur
ABC Score [Nunez 2009]	Penetrating Mechanism Systolic BP Heart Rate FAST ultrasound
McLaughlin Score [McLaughlin 2008]	Heart Rate Systolic BP pH Hematocrit
Traumatic Bleeding Severity Score [Ogura 2014]	Age Systolic BP FAST ultrasound Pelvic Fracture Severity Lactate

the sole outcome of interest fails to account for survivorship or competing risks bias [19]. For example, a patient presenting with an obvious severe deficit or bleeding source may be expedited quickly to surgery or embolization for hemostasis before meeting the required blood product threshold for massive transfusion. Our recent systematic review of clinical prediction models for traumatic hemorrhage demonstrate that (1) there are currently no clinical prediction models evaluating the composite outcome of interest, (2) many of the existing models were designed to identify only those requiring massive transfusion, (3) the existing literature generally failed to adhere to appropriate methodological standards [17].

2.5 Clinical Prediction Modeling

Given these considerations, there exists a clear need to standardize the evaluation and management of traumatic hemorrhage in a manner that allows for incorporation of existing evidence, improvement of safety and efficiency, and reduction in practice variability. Clinical prediction models are methods of studying predictors in order to identify existing disease (diagnostic) or future occurrence of disease (prognostic) [20]. In principle, models interpret patterns in existing data points with the intention of applying them in order to predict future data points. These models can be based off single or multiple predictors identified from clinical data, laboratory tests or other diagnostic studies [21]. Within medicine, they can be used to identify high risk populations for preventive interventions, provide decision support for diagnostic or therapeutic interventions, or provide prognostic information. Well-known examples include the Canadian CT Head Rule for use of CT in patients with minor head injury [22] and the Canadian C-Spine Rule for use of radiography in patients with blunt head and neck trauma [23]. This standardization of data gathering and interpretation reduces uncertainty in clinical decision making and informs practice based on the best available evidence [24].

To raise the quality of methodology for clinical prediction modeling, the Prognosis Research Strategy (PROGRESS) group provides evidence-based guidelines for the appropriate derivation, validation and implementation for such studies [25]. Prediction models are most successful when they are derived from a sufficiently robust, reliable dataset, based on a formalized study protocol and externally validated on a separate population [21]. Models should be created based on pre-specification of clinically important predictors based on the best available knowledge [25]. In the ideal setting, models should be derived, prospectively assessed for accuracy and reliability and then assessed for impact on patient care. This standardization of

data gathering and interpretation reduces uncertainty in clinical decision making and informs practice based on the best available evidence [24].

However, despite the increasing popularity of clinical prediction modeling research, the methodological standard for existing work is often quite poor [20]. Common lapses in quality include failure to consider previous work, selection of candidate predictors based on bivariable association testing, as well as small sample sizes and the resultant overfitting of data. While most studies describe model derivation, few will actually report external validation and even fewer will evaluate clinical impact [25]. A recent systematic review noted that prediction modeling studies often had unclear study designs, insufficient numbers of events for the number of selected predictors and categorized predictors. In addition, many studies failed to report key model performance measures. For these reasons, many prediction models exist but few are readily integrated into clinical practice. An ideal prediction modeling study should therefore strive for strong methodological quality and transparent reporting of model specification, estimation and performance [25]. The successful derivation, validation and implementation of a prediction model for the identification of bleeding patients would allow for more appropriate risk stratification and quicker activation of care pathways. The improved efficiency for triaging patients would theoretically reduce bleeding associated morbidity and mortality.

2.6 Chapter 2 References

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Chapter 3 – A Systematic Review of Clinical Prediction Models for Identifying Patients Requiring Major Intervention in Traumatic Hemorrhage

This chapter incorporates the protocol manuscript "Early identification of patients requiring massive transfusion, embolization or hemostatic surgery for traumatic hemorrhage: a systematic review protocol" and the review manuscript "A systematic review and meta-analysis of clinical prediction models for the early identification of the need for major intervention in traumatic hemorrhage". In accordance with the PROGRESS recommendations, this systematic review is conducted to identify candidate predictor variables from high quality studies in order to inform predictor selection of our own model in the upcoming derivation study.

3.1 Early Identification of Patients Requiring Massive Transfusion, Embolization or Hemostatic Surgery for Traumatic Hemorrhage: A Systematic Review Protocol

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Abstract

Background: Hemorrhage is a major cause of early mortality following a traumatic injury. The progression and consequences of significant blood loss occur quickly as death from hemorrhagic shock or exsanguination often occurs within the first few hours. The mainstay of treatment therefore involves early identification of patients at risk for hemorrhagic shock in order to provide blood products and control of the bleeding source if necessary. The primary objective of this systematic review is to identify and critically assess any existing multivariable models predicting significant traumatic hemorrhage that requires intervention, defined as a composite outcome comprising massive transfusion, surgery for hemostasis or angiography with embolization.

Methods: We will search the EMBASE and MEDLINE databases for all randomized controlled trials, prospective and retrospective cohort studies developing or validating predictors of intervention for traumatic hemorrhage in adult patients 16 years of age or older. Eligible predictors must be available to the clinician during the first hour of trauma resuscitation and may be clinical, lab-based or imaging-based. Outcomes of interest include need for surgical intervention, angiographic embolization or massive transfusion within the first 24 hours. We will evaluate these models for usefulness, applicability and the potential for external validation and updating in other populations. Given the anticipated heterogeneity in terms of variable definitions and categorization thresholds, we intend to focus on narrative description. The intended scope of this review is to identify and assess combinations of predictors informing therapeutic decision making for clinicians during the initial trauma assessment.

Discussion: This systematic review will summarize the evidence for predictors identifying the need for intervention in patients with traumatic hemorrhage.

Systematic Review Registration: PROSPERO CRD42017054589

Keywords: traumatic hemorrhage, prediction model, massive transfusion, surgery, embolization

Background

Traumatic Hemorrhage and its Consequences

Significant hemorrhage following a traumatic injury progresses quickly within the first few hours and can result in significant morbidity or mortality [1]. It is responsible for the majority of deaths in the operating room and nearly half of all deaths within the first 24 hours following an injury [2]. The early recognition and management of bleeding is paramount as unrecognized or uncontrolled hemorrhage is the leading cause of potentially preventable death among this patient population [3]. Following injury, tissue trauma and systemic hypoperfusion is thought to result in trauma-induced coagulopathy – a "global failure" of the coagulation system characterized by anticoagulation and hyperfibrinolysis [4]. Matters are further complicated by the frequent pathophysiological association of hypothermia, acidosis and coagulopathy following a major traumatic injury, aptly termed the "triad of death" [5]. These interactions result in an exaggerated bleeding state which when not lethal, can also lead to massive consumption of blood products and risk of significant morbidity.

Ongoing bleeding that is not rapidly identified and corrected results in a state of global hypoperfusion which in turn can lead to multiple organ dysfunction or failure [6]. The mainstay of treatment therefore involves early identification of patients at risk for hemorrhagic shock in order to provide packed red blood cells, platelets and clotting factors as well as hemostatic intervention such as embolization or surgery [7]. The importance of appropriate patient stratification within the first minutes to hours of resuscitation cannot be overstated [7].

Current Tools Used for Prediction of Hemorrhage

The Advanced Trauma Life Support (ATLS) guidelines provide an algorithmic approach, adapted worldwide, to the initial assessment and resuscitation of the trauma patient [8]. The

guidelines classify traumatic hemorrhage into four distinct classes of increasing severity based on clinical examination and alterations in baseline vital signs (Table 1). Proposed thresholds for resuscitation with crystalloid fluids or blood products are provided. However, these guidelines have come under greater scrutiny and criticism in recent years. A large database validation using the Trauma Audit and Research Network in the United Kingdom demonstrated that the ATLS guidelines overestimate the degree of tachycardia and hypotension associated with increasing blood loss [9]. In other words, significant blood loss can occur insidiously before obvious disturbances in vital signs appear. Similarly, another multi-centre database validation using the Trauma Registry of the German Society for Trauma Surgery found that less than 10% of patients could be classified accurately according to the ATLS guidelines [8]. The remaining patients demonstrated conflicting clinical parameters that would not permit for classification into any ATLS class of hemorrhage. It is not surprising then that in a 2012 international survey of ATLS course directors and instructors, only 10.9% of respondents stated that they considered the ATLS classification of hemorrhagic shock to be a "good guide for fluid resuscitation and blood product transfusion" [10].

In recent years, several clinical prediction models for hemorrhage have been proposed. These include the Trauma Associated Severe Hemorrhage (TASH) Score [11] or the Assessment of Blood Consumption (ABC) Score [12] for early prediction of patients requiring massive transfusion. However, the need for massive transfusion does not account for all clinically significant outcomes related to hemorrhage and when used in isolation, is prone to competing risks bias and survivorship bias [13]. Consider that any patient with significant bleeding may be identified quickly and offered a hemostatic intervention such as embolization or surgery long before meeting blood product utilization thresholds for massive transfusion. For this reason, any

prediction model for traumatic hemorrhage should seek to evaluate the totality of clinically significant outcomes related to bleeding in order to minimize bias.

Why it is important to do this review

While some patients arrive in hospital with an obvious need for early intervention, a subset of the trauma population does not manifest the classical clinical or biochemical extremes at presentation that prompt urgent action. It is this group in particular that is at risk of having their degree of hemorrhagic injury underestimated and therefore requires a systematic, evidence-based approach to early diagnosis. There is literature to suggest that elderly patients are significantly more prone to having massive bleeding missed on primary survey due to the absence of vital sign abnormalities and high incidence of non-cavitary, multi-site bleeding [14]. Unfortunately, there exists little in the way of commonly used alternatives to the ATLS classification for guiding clinical decision making in traumatic hemorrhage. Much of the existing work in this field focusses primarily on prediction models evaluating the need for massive transfusion as noted previously. However, this fails to capture the totality of clinically relevant interventions for hemorrhage, such as the need for hemostatic surgery or angiography with embolization. While a multitude of predictors have been studied with varying levels of success, there remain no widely adopted, evidence-based guidelines for their collective use. Development of such a decision-making framework to allow for early identification of patients needing interventions for hemorrhage would require a meticulous understanding of the existing clinical prediction literature. The recent Prognosis Research Strategy (PROGRESS) series recommendations note that the current methodological standard for modeling research is quite poor and needs to be improved [15]. Most new publications in this field describe only model development with very few considering external validation of previously developed models or

evaluating clinical impact. For the procurement of reliable and clinically useful models, it is recommended that they be developed from large, high quality datasets and validated externally in a separate population. Therefore, the PROGRESS investigators argue that any new modeling endeavors should begin not from scratch, but instead with the systematic identification of existing models and consideration of potential for external validation or modernization.

Objective

The primary objective of this systematic review is to identify and critically assess any existing multivariable models predicting significant traumatic hemorrhage that requires intervention, defined as a composite outcome comprising massive transfusion, surgery for hemostasis or angiography with embolization. These are prognostic models intended to predict future events and inform therapeutic decision making. We will evaluate these models for usefulness, applicability and the potential for external validation and updating in our population. Given the anticipated paucity of literature on this topic, this systematic review is intended to be inclusive, exploratory and descriptive in nature. The scope of this review is to identify and assess a specific combination of predictors informing therapeutic decision making for clinicians during the initial trauma assessment. If no existing models meeting our pre-specified criteria are identified, we will then secondarily identify potential candidate predictors for future derivation of a new prediction model.

Methods/Design

Protocol Registration

This systematic review protocol was designed using the Preferred Reporting Items for Systematic Review and Meta-Analyses Protocol (PRISMA-P) checklist [16] as well as the

Critical Appraisal and Data Extraction for Systematic Reviews of Modeling Studies (CHARMS) checklist [17]. The protocol has been registered with the PROSPERO International Prospective Register of Systematic Reviews (PROSPERO CRD42017054589)

Population

We will include all studies examining adult patients, aged 16 years or older presenting to hospital with a traumatic injury. Blunt or penetrating mechanisms of injury involving the thorax, abdomen or pelvis will be acceptable. Studies evaluating only patients with isolated head injury or isolated limb injuries will be excluded.

Predictors

Multivariable models will be eligible if they include any predictors typically available to the clinician during the first hour of the trauma assessment in the Emergency Department. This includes any pre-hospital or in-department variables. For the purposes of this review, these will include lab-based predictors such as the complete blood count, blood gases and coagulation tests. Any concerns regarding time of availability for a laboratory test will be reviewed with a clinical expert in laboratory medicine to determine eligibility. Clinical predictors will include vital signs and point-of-care cardiopulmonary testing such as heart rate variability. Imaging-based predictors will include focussed assessment with sonography in trauma (FAST) ultrasound or computed tomography (CT) scanning. Scoring or injury classification systems that are applied retrospectively (injury severity score, abbreviated injury scale) will be excluded. Reliance on serial measurements following an admission will be excluded. There is no pre-defined categorization of these variables and they will be extracted as defined by the study authors. The model is intended to be used at the time of initial trauma assessment and resuscitation in the ED.

Outcomes

The outcome is defined as the need for any life-saving intervention for traumatic hemorrhage, which serves as a surrogate for clinically significant bleeding. This includes need for hemostatic surgical intervention, angiographic embolization or massive transfusion within the first 24 hours in hospital. Studies describing surgeries without a documented indication or for non-hemorrhagic reasons, such as hollow viscus perforation, will be excluded. Angiography without embolization will similarly be excluded. There exist a variety of definitions of massive transfusion within the literature including: 10 units over the first 6, 12 and 24 hours or complete circulating volume over 24 hours [18]. We will include all of these definitions. There is no minimum number or percentage of patients receiving intervention (events) needed for inclusion in this review. The events-per-predictor evaluated will be captured as measure of statistical quality [17].

Study Design

We will include all clinical study designs evaluating predictors for life-saving intervention in traumatic hemorrhage, including randomized studies and cohort studies. There will be no date or language restrictions. Attempts will be made to translate any foreign language papers. This systematic review is primarily intended to identify and evaluate existing multivariable prediction models for our composite outcome of interest. If we are unable to find studies describing the composite outcome, we will include any models evaluating any of our individual outcomes of interest whether developmental, internally validated or externally validated.

Search Strategy and Data Sources

A comprehensive search strategy was developed in tandem with a health information specialist with expertise in systematic reviews and a clinical expert in the field of trauma. Individual search strategies were created for the EMBASE and MEDLINE databases and are available in Appendix 1 and Appendix 2 respectively. We used a combination of MESH terms and derived key words in order to define the trauma population and interventions of interest. We utilized an animal studies filter as suggested by the Cochrane Collaboration [19]. The reference lists of included studies or systematic reviews will be manually reviewed to ensure a comprehensive search. The clinicaltrials.gov registry and Central Cochrane Library databases will also be reviewed to identify unpublished or in-progress studies. In addition, we will search the conference abstracts of the past 3 years for the Trauma Association of Canada, the American Association for the Surgery of Trauma, the Eastern Association for the Surgery of Trauma, and the Trauma, Critical Care and Acute Care Surgery annual meetings.

Study Selection Process & Data Extraction

The literature results will be captured and uploaded to Covidence, a web-based reference manager, for facilitation of screening (online version, Albert Health) [20]. The screening process will involve two independent reviewers for title and abstract screening followed by full text screening with disagreements resolved by a senior reviewer. Abstracts selected by at least one reviewer will be obtained in full for evaluation.

Data extraction will be performed independently by the two reviewers using a pre-defined and piloted data collection form. Abstracted data will include publication characteristics (title, year of publication, author), patient and institution demographics (study inclusion criteria, trauma center level, civilian or military population). For multivariable models, we will extract

model characteristics such as included model type, predictor variables included, sample size, handling of missing data, model development, validation technique, performance (calibration, discrimination, sensitivity, specificity, positive predictive value, and negative predictive value) as well as model presentation and interpretation as suggested by the CHARMS guidelines [17]. For studies reporting preliminary bivariable testing as well as multivariable models, we will only report on the final derived model.

Data Synthesis, Meta-Bias & Confidence

If any suitable multivariable prognostic models for our composite outcome of interest are identified, the quality of each identified multivariable model will be described based on the items recommended by the CHARMS checklist [17]. In particular, we will describe the appropriateness of the outcomes and predictors, techniques used for predictor selection, sample size in terms of events per predictor, handling of missing data, model development, validation technique and measures of model performance. Quality assessment will be presented descriptively in summary table format only, as demonstrated in Table 1, and will be used to inform the selection of one or more suitable candidate models for external validation in our study population. As the primary objective of the review is to identify models for external validation in our study population, pooling or meta-analysis is not of interest.

Should no multivariable prediction models for our composite outcome be identified, we will secondarily seek to identify potential candidate predictors for a planned prediction rule derivation study. To inform the selection of candidate predictors for this derivation study, we will tabulate the frequency of use of each candidate predictor among the studies identified in our review, as a measure of potential importance of each predictor. We will also extract measures of

predictor-outcome associations (i.e., odds ratios) from any bivariable or multivariable tests involving any of the three outcomes comprising our composite. For predictors used in multivariable models meeting adequate quality criteria across multiple studies (e.g., at least 10 events per predictor), strength of association will be described using individual Forest Plots. Statistical heterogeneity will be examined using I^2 statistics [21]. While significant clinical and statistical heterogeneity is expected across studies (e.g., in terms of definitions of predictors and outcomes, categorization of predictors, the types of models used), pooling of odds ratios using meta-analysis is not anticipated. In the event that meta-analysis is deemed appropriate, pooled measures of association will be calculated using random-effects meta-analysis. These results will be used solely to inform the pre-specification of important clinical predictors for consideration in the planned clinical derivation study.

There are no planned assessments of meta-bias or strength of evidence statements.

Discussion

The assessment of patients for significant traumatic hemorrhage can prove quite challenging and at times overwhelming. The clinician is tasked with processing inputs from a plethora of clinical, lab-based and diagnostic imaging-based data sources and utilizing them in a manner that allows for rapid identification of patients at risk of significant bleeding. When such a scenario is rapidly and correctly identified, the patient is able to receive a much needed intervention – often in the form of transfusion, surgery or angiography. In this systematic review, we will rigorously identify, describe and summarize the existing literature evaluating predictors of intervention in patients with traumatic hemorrhage.

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Appendix 1 – EMBASE Search Strategy

OVID EMBASE Search Strategy

1. trauma.mp
2. (trauma* or polytrauma*).tw
3. exp abdominal injury
4. exp penetrating trauma
5. exp blunt trauma
6. exp crush trauma
7. exp multiple trauma
8. exp traumatic amputation
9. exp traumatic shock
10. or/1-9
11. h?morrhag*.tw
12. transfus*.tw
13. intervention.tw
14. surger*.tw
15. angiogra*.tw
16. laparotomy.tw
17. thoracotomy.tw
18. estimated blood loss.tw
19. or/11-18
20. predict*.ti
21. model*.ti
22. utility.ti
23. scor*.ti
24. validation.ti
25. or/20-24
26. 10 and 19 and 25
27. animals/not humans/
28. 26 not 27

Appendix 2 – Medline Search Strategy

OVID MEDLINE Search Strategy

1. "wounds and injuries".mp
2. trauma.mp
3. (trauma* or polytrauma*).tw
4. exp wounds, nonpenetrating
5. exp wounds, penetrating
6. exp multiple trauma
7. exp shock, traumatic
8. exp amputation, traumatic
9. exp blast injuries
10. exp abdominal injuries
11. exp thoracic injuries
12. exp war-related injuries
13. or/1-12
14. h?morrhag*.tw
15. transfus*.tw
16. intervention.tw
17. surger*.tw
18. angiogra*.tw
19. laparotomy.tw
20. thoracotomy.tw
21. estimated blood loss.tw
22. or/14-21
23. predict*.ti
24. model*.ti
25. utility.ti
26. scor*.ti
27. validation.ti
28. or/23-27
29. 13 and 22 and 28
30. (animals not humans.sh)
31. 29 not 30

3.2 Early Identification of Patients Requiring Massive Transfusion, Embolization or Hemostatic Surgery for Traumatic Hemorrhage: A Systematic Review and Meta-Analysis

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Abstract:

Background: Delays in appropriate triage of bleeding trauma patients result in poor outcomes. Clinical gestalt is fallible and objective measures of risk stratification are needed. The objective of this review is to identify and assess prediction models and predictors for the early identification of traumatic hemorrhage patients requiring massive transfusion, surgery or embolization.

Methods: We searched electronic databases through to September 31st, 2016 for studies describing clinical, laboratory and imaging predictors available within the first hour of resuscitation for identifying patients requiring major intervention for hemorrhage within the first 24 hours.

Results: We included 84 studies describing any predictor-outcome association, including 47 multivariable models; of these, 26 (55%) were specifically designed for prediction. We identified 35 distinct predictors of which systolic blood pressure, age, heart rate and mechanism of injury were most frequently studied. Quality of multivariable models was generally poor with only 21 (45%) meeting a commonly recommended sample size threshold of 10 events per predictor. From 21 models meeting this threshold, we identified 7 predictors that were examined in at least two models: mechanism of injury, systolic blood pressure, heart rate, hemoglobin, lactate and FAST. Pooled odds ratios were obtained from random-effects meta-analyses.

Conclusion: The majority of traumatic hemorrhagic prediction studies are of poor quality, as assessed by the PROGRESS recommendations and CHARMS checklist. There exists a need for a well-designed clinical prediction model for early identification of patients requiring intervention. The variables of clinical importance identified in this review are consistent with

recent expert guideline recommendations and may serve as candidates for future derivation studies.

Level of Evidence: Systematic review, Level III

Keywords: traumatic hemorrhage, prediction modeling, massive transfusion, surgery, embolization

Background:

Traumatic exsanguination progresses rapidly with the majority of deaths occurring in the first 6 – 12 hours[1, 2] and very few after the first day[3]. As the degree of blood loss increases, this is accompanied by severe derangements in physiology including acidosis, coagulopathy and hypothermia[3]. This "triad of death" acts synergistically to further exacerbate the already grave bleeding state[4]. In a study evaluating trauma-related mortality at a Level 1 Canadian Trauma Center, the authors note that up to 16% of hemorrhagic deaths were believed to be preventable due to significant delays in identifying the source of bleeding[5]. Despite improved regionalisation of trauma systems facilitating transfer to specialized trauma centers and decreasing national trends of injury in the United States, up to 7% of patients presenting in extremis ultimately die from a surgically correctable single system injury[6]. Unfortunately, there are no existing, well-validated tools for such a purpose at the current time. In recent years, the Advanced Trauma Life Support (ATLS) guidelines have come under great scrutiny after a number of validation studies demonstrated poor overall accuracy[7] and consistent overestimation of associated vital sign derangements during significant bleeding[8].

It is clear that the early identification and control of hemorrhage "remains a major cornerstone of modern trauma care" [5]. These interventions may include resuscitation with blood products or hemostatic procedures such as surgery or embolization [9]. Much of the existing clinical prediction work for traumatic hemorrhage focusses on massive transfusion as the sole outcome of interest[10, 11]. However, concept of massive transfusion is known to be prone to survivorship and competing risk bias[12] as patients with significant bleeding at presentation may either die or receive a hemostatic intervention long before meeting the threshold definition of

massive transfusion. Therefore, prediction models for traumatic hemorrhage should account for these considerations using either competing risk adjusted analyses or composite outcomes.

The adoption of a simple, well-validated prediction model for the early identification of patients requiring intervention for traumatic bleeding would improve clinical assessment and reduce the incidence of preventable deaths. In accordance with the Prognosis Research Strategy (PROGRESS) series recommendations, any prediction modeling study should begin with the systematic identification of existing models and consideration of their potential for validation or modernization[13]. Therefore, the primary objective of this review is to identify and critically assess any existing multivariable models predicting significant traumatic hemorrhage that requires intervention, defined as a composite outcome comprising massive transfusion, surgery for hemostasis or angiography with embolization. The intended scope of this review is to identify and assess a specific combination of predictors informing therapeutic decision making for clinicians during the initial trauma assessment, and evaluate these models for usefulness, applicability and the potential for external validation and updating in our population. If no existing prediction models are identified, the review will be used to identify individual candidate predictors for future derivation of a high quality prediction model.

Methods

This systematic review was conducted based on a previously published protocol [14] and was registered with the International Prospective Register of Systematic Reviews (PROSPERO # CRD42017054589). This review has been prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement[15] as well as the Critical

Appraisal and Data Extraction for Systematic Reviews of Modeling Studies (CHARMS) Checklist[16].

Scope of this review

This systematic review is primarily intended to identify and evaluate existing multivariable prediction models for our composite outcome of interest. In the event that no multivariable models are identified, the review will be used to identify models evaluating any of our individual outcomes of interest whether developmental, internally validated or externally validated. It will also be used to evaluate individual predictors for any of our outcomes of interest based on any available tests of predictor-outcome association. This includes bivariable testing and multivariable modeling for any of the three outcomes comprising our composite.

Study Eligibility Criteria

Models of interest are those intended for use at the time of initial trauma assessment and resuscitation.

Population: We included studies of adult patients, 16 years of age or older with traumatic injuries. We excluded studies of patients with isolated head injury without torso involvement, isolated traumatic limb amputations, isolated long bone fractures or burn injuries.

Predictors: We included studies evaluating any clinical, laboratory or imaging predictors typically available to the clinician during the initial hour of resuscitation for the trauma patient. This includes any prehospital or in-department predictors. Studies which used scoring or classification systems applied retrospectively (Injury Severity Score) were excluded. Studies which relied on serial measurements following an admission were excluded. The appropriate

exclusion of studies based on timing of availability for laboratory tests were reviewed with a clinical expert in laboratory medicine to determine eligibility. There was no pre-defined categorization of any continuous predictors and associations were extracted as described by the study authors.

Outcomes: Eligible studies examined the outcome defined as need for any life-saving intervention for traumatic hemorrhage, which serves as a surrogate for clinically significant bleeding. This includes need for hemostatic surgical intervention, angiographic embolization or massive transfusion (as defined by study authors) within the first 24 hours in hospital. Studies that define the outcome as surgery without a documented indication or for non-hemorrhagic reasons, such as hollow viscus perforation, or as angiography without embolization, were excluded.

Study Design: All clinical studies evaluating predictors for intervention in traumatic hemorrhage including randomized controlled trials, cohort studies and case control studies were eligible. In order to maximize inclusiveness, no distinction was made between studies designed for assessment of association versus prediction.

Search Strategy & Data Sources

We searched the MEDLINE and EMBASE databases from January 1st, 1946 – September 31st, 2016 using a pre-defined search strategy developed under the guidance of a health information specialist with expertise in systematic reviews and a clinical expert in the field of trauma (JL, MM). The search strategy[14] included a combination of MESH terms and derived key words in order to define the trauma population and interventions of interest. There were no date or language restrictions. To identify grey literature, we hand-searched the reference lists of all

included studies or systematic reviews, Central Cochrane Library databases as well as the conference abstracts of the past 3 years for the Trauma Association of Canada, the American Association for the Surgery of Trauma, the Eastern Association for the Surgery of Trauma and the Trauma, Critical Care and Acute Care Surgery annual meetings. We additionally searched the clinicaltrials.gov registry for any studies in progress.

Study Selection & Data Collection

Two authors (AT and MM) participated in abstract and full-text screening, independently and in duplicate, using an online reference manager[17]. Any disagreement was discussed among reviewers for consensus and if unsuccessful, a third party reviewer was consulted (JL). Kappa agreement was 0.76 (95% confidence interval (CI) 0.72 to 0.80) for abstract screening and 0.78 (95% CI 0.70 to 0.86) for full-text screening. The study selection process is summarized in a PRISMA flow diagram (Figure 1). Extracted data included publication characteristics as well as patient and institution demographics. We additionally extracted predictors of interest, model characteristics and quality assessment metrics for multivariable models.

Quality Assessment

Multivariable models were assessed for quality using criteria modified from the work by Perel et al[18] as well as the items identified in the CHARMS checklist[16]. We assessed metrics including clarity of patient population and predictor definition, sample size in terms of events per predictor (EPV), model building strategies and presentation of findings. We defined a model to be of acceptable quality for quantitative analysis if it included at least 10 events per variable (EPV > 10) [19]. It is well known that models developed from datasets with low EPV ratios are

likely to lead to biased coefficient estimates, overfitting of the developmental dataset and poor performance during external validation[20].

Data Presentation & Synthesis

The frequency of use for each predictor across studies was tabulated as a measure of potential importance and research interest. For predictors used in acceptable quality multivariable models, strength of association was described using forest plots. Pooled measures of association plus 95% confidence intervals were calculated using random-effects models[21]. Prediction intervals were additionally calculated for variables with more than 3 studies[22]: in contrast to the 95% confidence interval which provides the average summary measure of association across the distribution of observed associations, the prediction interval describes the range of expected effect measures in future studies.

Results:

Study Selection

A total of 3,548 records were identified and screened from which 84 studies met criteria for inclusion in this review (see Figure 1). Reasons for exclusion are provided in the PRISMA flow diagram.

Study Characteristics

Summary characteristics of included studies are presented in Table 1. The complete reference list of all included studies is provided in Appendix 1. All but one study[23] were published in the year 2000 or later. All included studies utilized a cohort design: 20 were prospective, 63 retrospective and one indeterminate. There were 17 (20.2%) multi-centre studies.

The majority of studies (65.5%) involved either United States civilian or military populations. There were 78 studies (92.9%) evaluating civilian populations and 6 studies (7.1%) evaluating military populations. Sample size ranged from 38 to 17,988 patients with a median (IQR) of 484.5 (956). All of the reported participating centers were designated as Level 1 trauma, major or university hospitals. There were 9 studies (10.7%) evaluating only patients with blunt mechanism of injury. The most common additional inclusion criteria were direct arrival from scene (19.0%), highest level trauma team activation (12.2%), intensive care admission requirement (9.5%) and injury severity scale (ISS) $\geq$ 16 (8.3%).

None of the studies evaluated the composite interest for our primary objective. There were 62 studies (73.8%) evaluating massive transfusion as the sole outcome, 6 studies (7.1%) evaluating hemostatic surgery, 6 studies (7.1%) evaluating embolization and 10 studies (12.2%) evaluating multiple outcomes.

Types of Predictors

We identified 35 distinct predictors across all included studies, that is, clinical, laboratory or imaging-based predictors that would be typically available to the clinician during the initial hour assessment and resuscitation in the emergency department. The frequency of use of each predictor across all included studies is tabulated in Figure 2 and further characterized by whether evaluation was performed using multivariable or single variable analysis. The most commonly used predictors across all statistical analysis methods included systolic blood pressure (BP) (n = 26), age (n = 19), heart rate (n = 18), mechanism of injury (n = 17), hemoglobin (n = 17), base deficit (n = 13), lactate (n = 13), and International Normalized Ratio (INR) (n = 13).

Types of Models

From the 84 included studies, we identified 47 distinct multivariable models across 46 studies. The remaining studies evaluated single predictors only. The individual predictor compositions for these models are summarized in Table 2. There were 37 models (78.7%) evaluating massive transfusion as the sole outcome, 3 models (6.4%) evaluating surgery, 2 models (4.3%) evaluating embolization and 5 (10.6%) evaluating multiple outcomes. The most frequently examined predictors were systolic BP (n = 33), heart rate (n = 20), hemoglobin (n = 14), base deficit (n = 14), age (n = 11), INR (n = 10), pelvic instability (n = 8) and Focussed Abdominal Sonography for Trauma (FAST) (n = 8).

Quality Assessment

Only 26 models (55 %) were primarily designed for the purpose of prediction while the remaining models were utilized for confounding adjustment in the evaluation of a single predictor (Table 3). All studies provided a clear definition of the study population. Only 15 (32%) provided justification for their selection of predictors and only 30 studies (64%) provided a clear definition of predictor measurement. Handling of missing data was frequently not reported (70%) and the most common method was complete-case analysis or list-wise exclusion (28%). The most common method for predictor selection was forward, backward or stepwise (40%) while 10 studies (21%) did not report the use of any selection method. Statistical interactions were rarely examined (4%). The majority of studies (53%) categorized continuous variables. Only 21 studies (45%) met the recommended threshold of 10 or more events per variable. Four of the models (9%) were externally validated at the time of the index study while 10 studies (21%) described some form of internal validation. The remaining models were either not validated or not designed for the purposes of prediction. The majority of model presentations (66%) did not present complete information such as an estimated regression equation that would

allow users to calculate predicted risk while the most common form of presentation was conversion to a simplified score (15%). Because there were no multivariable models identified for our composite outcome of interest, we chose not to extract overall model performance metrics such as discrimination and calibration for the purpose of describing individual predictors.

Data Synthesis

Among the 21 models identified for quantitative analysis (see Table 2), 18 evaluated massive transfusion as a sole outcome, two models evaluated surgery and one model evaluated surgery and embolization. We identified 7 predictors that were evaluated in two or more acceptable quality models: mechanism of injury, systolic BP, heart rate, hemoglobin, lactate, INR and FAST. Forest plots synthesizing the strength of association for these predictors are presented in Figure 3. Heterogeneity between estimates was substantial, with I^2 statistics > 75% for 5 of 7 predictors (mechanism of injury, systolic BP, heart rate, hemoglobin and FAST).

Mechanism of Injury

We identified 6 acceptable quality models describing mechanism of injury as a predictor[11, 24, 25, 26, 27, 28]. All of the odds ratios for each study were ≥ 1, favouring penetrating over blunt mechanism as a significant risk factor and the pooled odds ratio was 1.88 (95% CI 1.23 to 2.88). The calculated 95% prediction interval was 0.46 to 7.69.

Systolic BP

We identified 6 acceptable quality models describing systolic BP as a predictor[2, 11, 24, 27, 29,30]. All of the odds ratios for each study were ≥ 1, favouring hypotension as a significant risk factor with pooled odds ratio 3.95 (95% CI 2.18 to 7.15). Hypotension was defined as systolic

BP ≤ 90 mmHg in 3 studies[11, 24, 27] and < 110 mmHg in 2 studies[2, 29]. One study described systolic BP at 4 levels: greater than 110 mmHg, between 100 and 110 mmHg, between 90 and 100 mmHg and less than 90 mmHg[30]. The odds ratio provided for this study describes the increased odds of intervention at for each one level increase in ordinal classification of hypotension and was therefore not included in the meta-analysis. The calculated 95% prediction interval was 0.47 to 33.53.

Heart Rate

We identified 7 acceptable quality models describing heart rate as a predictor [2, 11, 24, 25, 27, 29, 31]. All of the odds ratios for each study were ≥ 1, favouring tachycardia as a significant risk factor and the pooled odds ratio was 2.57 (95% CI 1.81 to 3.67). Tachycardia was defined as HR ≥120 in 3 studies[11, 24, 31], HR > 105 in 2 studies[2, 29], and HR > 100 in two studies[25, 27]. The calculated 95% prediction interval was 0.81 to 8.18.

Hemoglobin

We identified 3 acceptable quality models describing hemoglobin as a predictor[24, 26, 29]. All of the odds ratios for each study were ≥ 1, favouring anemia as a significant risk factor and the pooled odds ratio was 3.78 (95% CI 1.97 to 7.26). Anemia was defined as hemoglobin ≤ 110 in 2 studies[24, 29] and hemoglobin ≤ 115 in another[26].

Lactate

We identified 3 acceptable quality models describing lactate as a predictor[29, 30, 32]. All of the odds ratios for each study were ≥ 1, favouring severe lactic acidosis as a significant risk factor and the pooled odds ratio was 4.10 (95% CI 2.50 to 6.74). Severe lactic acidosis was

defined as lactate ≥ 5 in one study[29] and lactate > 7.5 in another[32]. One study[30] described lactic acidosis at 4 levels: less than 2.5, between 2.5 and 5.0, between 5.0 and 7.5 and greater than 7.5. The odds ratio provided for this study describes the increased odds of intervention at for each one level increase in ordinal classification of lactic acidosis and was therefore not included in the meta-analysis.

INR

We identified 2 acceptable quality models describing INR as a predictor[24, 29]. The odds ratios for each study were ≥ 1, favouring coagulopathy as a significant risk factor and the pooled odds ratio was 4.16 (95% CI 2.57 to 6.73). Coagulopathy was defined as INR > 1.5 in both studies[24, 29].

FAST

We identified 3 acceptable quality models describing FAST as a predictor[11, 24, 30]. The odds ratios for each study were ≥ 1, favouring a positive FAST as a significant risk factor and the pooled odds ratio was 4.29 (95% CI 1.29 to 14.28). The odds ratio provided for the Ogura et al. study[30] describes the increased odds of intervention at for each one level increase in number of FAST quadrants positive and was therefore not included in the meta-analysis.

Discussion:

This systematic review identified and described the current prediction modeling literature for early identification of patients requiring significant intervention for traumatic hemorrhage. We were unable to identify any high quality multivariable models evaluating our composite outcome of interest for massive transfusion, surgery and embolization. Therefore, we pursued

our a priori secondary objective of identifying and evaluating individual predictors based on strength of association measures extracted from acceptable quality multivariable models. Among 21 models meeting an appropriate sample size criterion (EPV > 10), we identified 7 predictors for further analysis. These predictors were independently validated as important risk factors in two or more acceptable quality models: mechanism of injury (penetrating), systolic BP (hypotension), heart rate (tachycardia), hemoglobin (anemia), lactate (severe lactic acidosis), INR (coagulopathy) and FAST (positive for free fluid).

Our review found that the overall quality of traumatic hemorrhage prediction literature was poor as assessed by methodological standards set forth by the PROGRESS recommendations[13] and the CHARMS checklist[16].We note frequent lack of justification of predictors, inadequate reporting or suboptimal handling of missing data, inadequate events per variable ratios, data driven methodology for predictor selection, inadequate validation, and incomplete model presentation. Failure to adhere to appropriate methodological standards for prediction studies leads to models that are prone to being overly optimistic and provide suboptimal results when applied to an external population[33].

Despite significant technological advancements in traumatic hemorrhage and early coagulopathy assessment, uncontrolled hemorrhage remains the primary cause of preventable death following injury[34], often due to fallibility of clinical judgment[34]and subsequent delays in identifying the major source of injury[5]. The most recent edition of the European Guidelines for Management of Major Bleeding and Coagulopathy following Trauma expectedly advocate for minimization of the time between injury and bleeding control[9]. Existing literature, expert opinion and current practice were considered in order to provide rationale for an evidence-based approach to the initial assessment and management of traumatic hemorrhage. Notably, all seven

of the risk factors identified in this systematic review received Grade 1 recommendations for incorporation into the routine evaluation of traumatic hemorrhage. The authors note that preliminary clinical assessment should be based on a combination of patient physiology (including systolic blood pressure and heart rate), anatomical injury pattern and mechanism of injury[9]. Screening laboratory investigation should include the use of initial hemoglobin for detection of severe bleeding and serial measurements for determination of ongoing blood loss. In addition, serum lactate and base deficit should be considered sensitive tests for estimation and monitoring of appropriate tissue oxygenation in the setting of hemorrhagic shock. The authors also advocate for the routine practice of early and repeated monitoring of coagulation parameters such as INR among others. Finally, Rossaint and colleagues recommend that early imaging such as FAST be used to rapid detection of free fluid in patients with suspected torso trauma.

The ability to accurately and efficiently identify patients with potentially significant hemorrhage would provide a valuable clinical tool for triage, assessment and determination of appropriateness for intervention[34]. This early recognition should prompt more aggressive stabilization which in turn may reduce mortality and improve outcomes[10]. The advocacy for the development and validation of an objective, evidence-based assessment method demonstrates a clear need for further work in this domain. The increasing importance and interest in this field is illustrated by the fact that no fewer than 54 of our 84 identified studies for traumatic hemorrhage prediction were published after 2010.

Limitations

To explore the existing literature for traumatic hemorrhage prediction, we intentionally adopted an inclusive and practical approach in designing our previously published protocol[14]. In

accordance with the PROGRESS recommendations, we sought to identify existing high quality models for validation or modernization[13]. After being unable to identify any such models, we secondarily focussed on identification and evaluation of individual predictors. Recognizing the pragmatic protocol design, we emphasize cautious interpretation and acknowledge the following limitations: First, the majority of our studies (n = 18 models) are cohort studies evaluating predictors for massive transfusion with some contribution from studies evaluating surgery (n = 2 models) and from studies evaluating multiple outcomes (n = 1 model). As noted by numerous previous work[12, 35], the concept of massive transfusion does not account for all clinically relevant outcomes related to hemorrhage and when used in isolation, is prone to competing risks bias and survivorship bias. It is for these reasons that we designed the protocol with an a priori defined composite outcome that minimizes these associated biases[14]. Second, we note some clinical heterogeneity with regards to differences in model specification and categorization thresholds for definitions such as tachycardia and hypotension. Furthermore, the I^2 statistics were > 75% for 5 of 7 predictors, which suggest substantial statistical heterogeneity between studies. As described by Riley et al.[22], correct interpretation of results from random effects meta-analysis recognizes that the summary measure reflects the average estimate of association across a distribution of studies in real world conditions, rather than an assumed common effect. We additionally calculated prediction intervals to describe the anticipated range of associations in future studies; however, due to a small number of studies and substantial between-study variation, the calculated prediction intervals were very wide. Despite these limitations, the frequency of investigation of these variables, and the consistency of directionality of effect across different studies, different categorization thresholds, and with different controlled covariates underscore the potential importance of these predictors for future derivation studies.

Conclusion:

There is no high quality, evidence-based prediction model for traumatic hemorrhage intervention. Future prediction rule derivation studies should adhere to appropriate methodological standards including justification and pre-specification of predictors using the best available knowledge and clinical expertise. The variables of clinical importance identified in this review, namely mechanism of injury, systolic BP, heart rate, hemoglobin, lactate, INR and FAST are consistent with recommendations provided by recent expert guidelines and may serve to inform future derivation of a much needed high quality prediction model. The successful validation and implementation of such as model would prove invaluable in the assessment and care of a high risk selection from the trauma population.

Figure 1 – PRISMA Flow Diagram for Study Selection Process

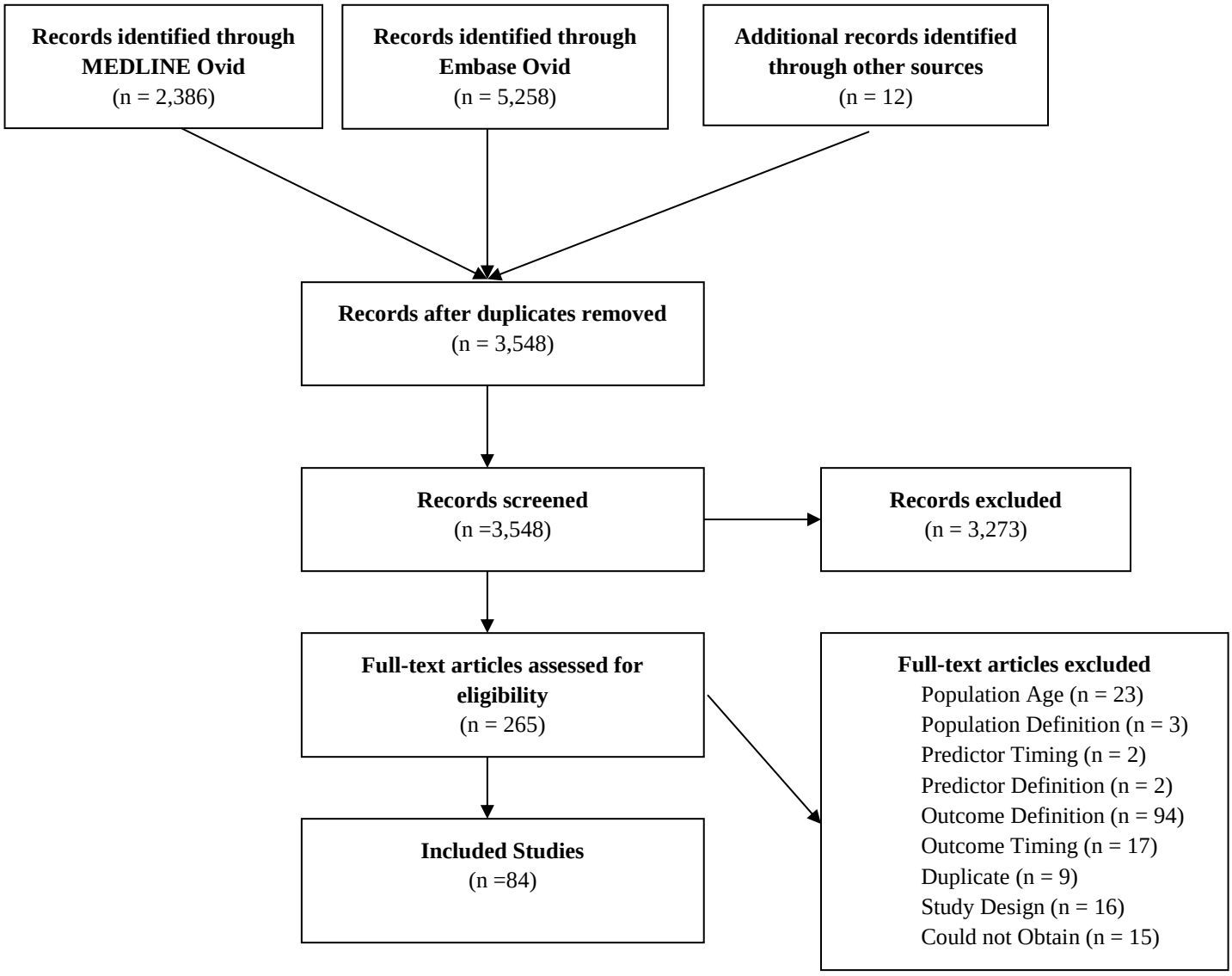


Figure 2 – Frequency of Use of Individual Predictors

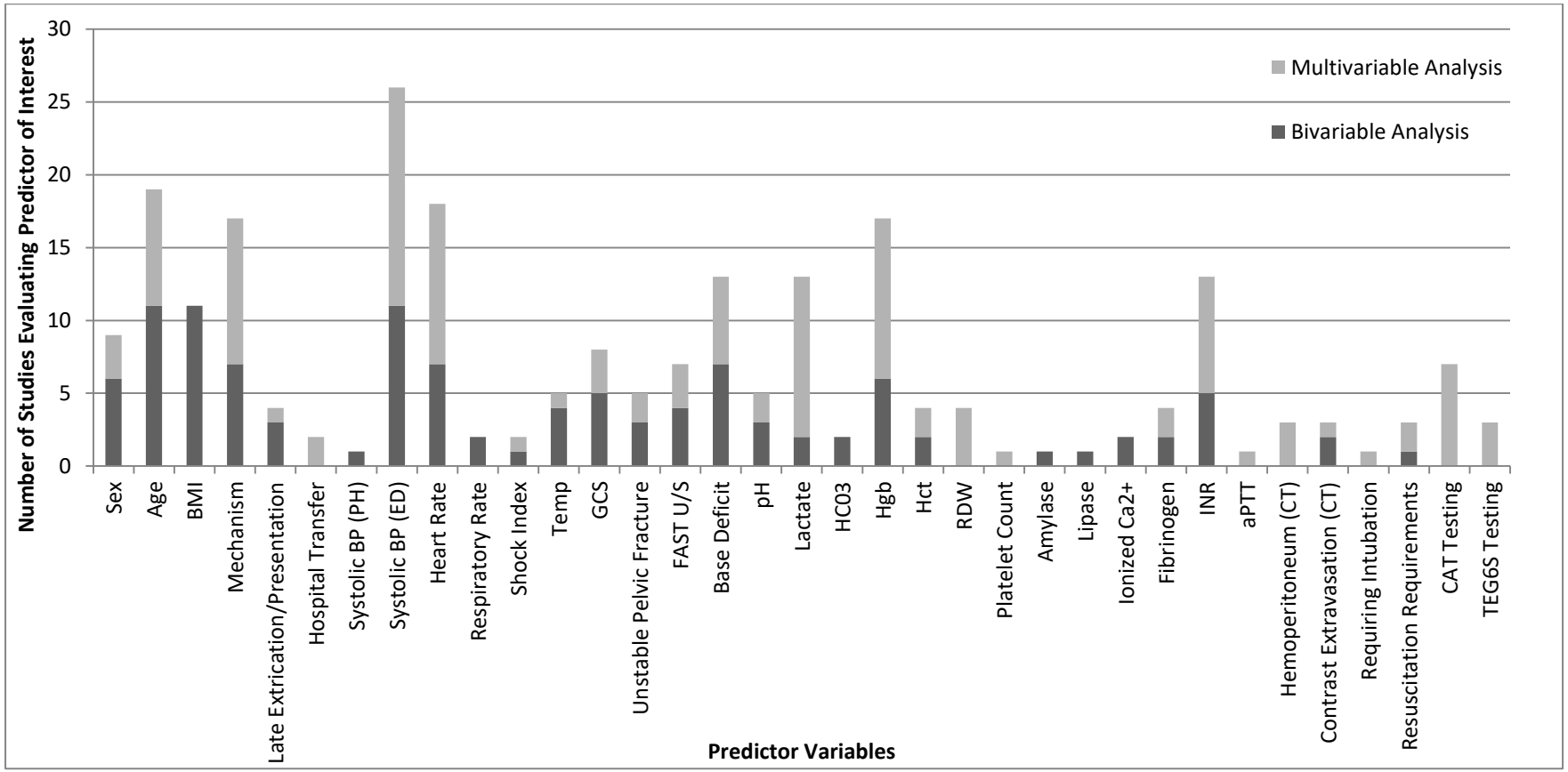
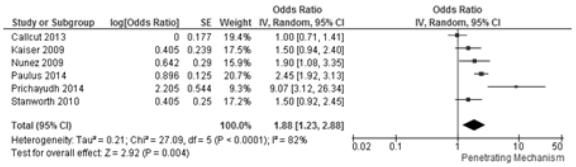
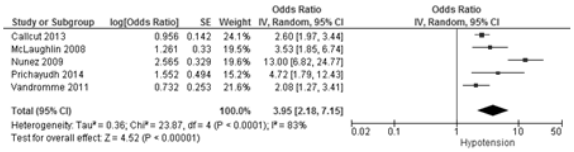


Figure 3 – Forest Plots for Individual Predictors

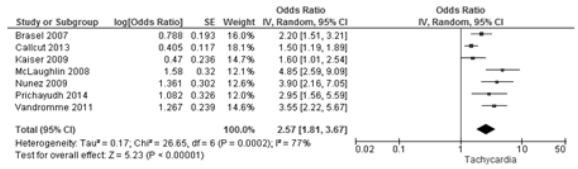
Mechanism of Injury



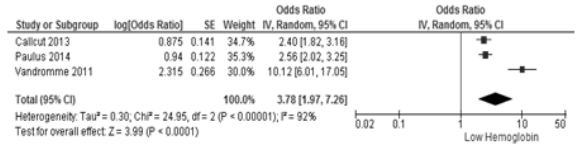
Systolic BP



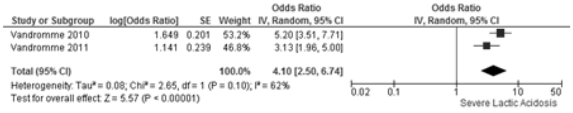
Heart Rate



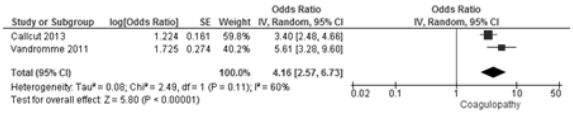
Hemoglobin



Lactate



INR



FAST

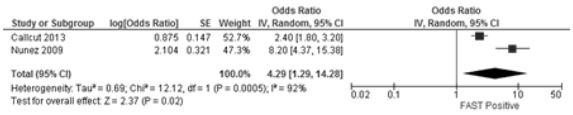


Table 1 – Study Characteristics of Included Studies (N = 84)

Description	N (%)
Country of Study	
USA	55 (65.5%)
Europe	13 (15.5%)
Asia	8 (9.5%)
Australia & New Zealand	6 (7.1%)
Other	2 (2.4%)
Year of Publication	
Before 2000	1 (1.2%)
2000 – 2005	5 (6.0%)
2006 – 2010	24 (28.6%)
After 2010	54 (64.2%)
Study Design	
Prospective Cohort	63 (75.0%)
Retrospective Cohort	20 (23.8%)
Indeterminate Cohort	1 (1.2%)
Sample Size, Median (IQR)	484.5 (956)
Population	
Civilian	78 (92.9%)
Military	6 (7.1%)
Mechanism	
Blunt Only	9 (10.7%)
Penetrating Only	0 (0%)
Any Mechanism	75 (89.3%)
Additional Inclusion Criteria	
Direct Arrival from Scene	16 (19.0%)
Highest Trauma Team Level Activation	10 (12.2%)
Requiring Intensive Care Admission	8 (9.5%)
Major Injury (ISS $\geq$ 16)	7 (8.3%)
Outcome of Interest	
Massive Transfusion Only	62 (73.8%)
Hemostatic Surgery Only	6 (7.1%)
Embolization Only	6 (7.1%)
Two or More Major Interventions	10 (12.2%)
All Three Major Interventions	0 (0%)

Table 2 – Composition of Multivariable Prediction Models

NS = included in model, not significant ($p \geq 0.05$), NR = included in model, significance not reported, ✓ = included in model, statistically significant ($p < 0.05$), . = not studied/included in model
MT = massive transfusion, EMB = embolization, SURG = surgery, * = Score developed for another population or outcome and applied by listed authors for MT prediction in adult trauma patients, † = high quality model (EPV > 10)

Author & Year	Outcome of Interest	Demographic			Clinical						Laboratory									Imaging			Other
		Sex	Age	Mech.	Sys BP	HR	SI	PRBC	GCS	Unstable Pelvis	HGB	BD	Lactate	pH	INR	aPTT	FBG	CAT	TEG	FAST	Extrav. (CT)	Hematoma (CT)	
Beekley 2010 [36]	MT	.	.	.	.	.	.	.	.	.	✓	.	.	.	✓	.	.	.	.	.	.	.	.
Bozeman 2012 [37]	EMB	.	✓	.	✓	.	.	.	.	NS	.	.	.	.	.	.	.	.	.	.	✓	NS	.
Brasel 2007 †[31]	SURG/EMB	.	✓	.	✓	✓	.	.	✓	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Brooke 2016 [38]	MT	.	.	NS	✓	.	.	.	NS	.	.	.	✓	.	.	.	.	.	.	.	.	.	.
Callcut 2013 (MTS)†[24]	MT	.	.	NS	✓	NS	.	.	.	.	✓	✓	.	.	✓	.	.	.	.	✓	.	.	.
Callcut 2016 (Revised MTS)†[39]	MT	.	.	.	NR	.	.	.	.	.	NR	NR	.	.	NR	.	.	.	.	.	.	.	Temp (NR)
Cancio 2008 (RTS*)†[40]	MT	.	.	.	NR	.	.	.	NR	.	.	.	.	.	.	.	.	.	.	.	.	.	Resp Rate (NR)
Cancio 2008 (FTS*)†[40]	MT	.	.	.	NR	.	.	.	NR	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Cardenas 2014 [41]	MT	NR	NR	.	.	.	.	.	.	.	.	NR	.	.	.	.	.	✓	.	.	.	.	.
Charbit 2013†[42]	MT	.	.	.	NR	.	.	.	.	NR	.	NR	.	.	.	.	.	.	.	.	.	✓	.
Chico-Fernandez 2011 (ETS*) [43]	MT	.	NR	NR	NR	.	.	.	.	NR	.	.	.	.	.	.	.	.	.	NR	.	.	Hospital Transfer (✓)
Costantini 2016 [44]	SURG/EMB	.	.	.	.	.	.	.	.	✓	.	.	.	.	.	.	.	.	.	.	.	.	.
Cotton 2011 [45]	MT	NS	NS	NS	NS	NS	.	.	.	.	.	.	.	.	.	.	.	✓	.	NS	.	.	.
Edla 2015 [46]	MT	.	.	.	NR	NR	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	Resp Rate NR) Pulse Pressure (NR) HR Variability (NR)
Guyette 2011 [47]	SURG/EMB	.	.	.	NS	.	.	.	.	.	.	.	✓	.	.	.	.	.	.	.	.	.	.
Hagiwara 2010 [48]	MT/SURG/EMB	.	.	.	.	.	✓	.	.	.	.	✓	.	.	.	.	.	.	.	.	.	.	
Holcomb 2012 [49]	MT	NR	NR	NR	.	.	.	.	.	.	.	NR	.	.	✓	✓	NS	.	✓	.	.	.	PLT (NS)
Kaiser 2009†[25]	SURG	.	.	NS	.	NS	.	✓	.	.	.	.	.	.	.	.	.	.	.	.	.	.	Time to ED (✓) Intubated (NS)
Leemann 2010 [50]	MT	.	.	.	.	.	.	.	.	.	✓	.	.	.	.	.	.	✓	.	.	.	.	.
Mackenzie 2014 [51]	MT	NR	NR	.	.	NR	NR	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	SpO2/HR Features (NR)
Matthew 2016 [52]	MT	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	✓	.	.	.	.
McCully 2014 [53]	MT	.	.	.	✓	.	.	.	.	.	✓	.	.	.	.	✓	.	.	.	.	.	.	.
McGuire 2011[54]	SURG/EMB	.	.	.	NS	NS	.	.	.	.	NS	.	.	.	.	.	.	.	.	.	.	.	.
McLaughlin 2008†[2]	MT	.	.	.	✓	✓	.	.	.	.	.	.	.	✓	.	.	.	.	.	.	.	.	Hct (✓)
Mitra 2012 (PWH Score*) [55]	MT	.	.	.	NR	NR	..	.	NR	NR	NR	NR	.	.	.	.	.	.	.	NR	.	.	.
Moore 2008†[56]	MT	.	.	.	✓	.	.	.	.	.	.	.	.	.	✓	.	.	.	.	.	.	.	Hospital Transfer (✓)
		.	.	.	✓	.	.	.	.	.	.	.	.	✓	.	.	.	.	.	.	.	.	Hospital Transfer (✓)
Nunez 2009 (ABC Score)†[11]	MT	.	.	✓	✓	✓	.	.	.	.	.	.	.	.	.	.	.	.	.	✓	.	.	.
Nunez 2010 [57]	MT	NS	NS	NS	.	.	.	✓	.	.	.	NS	.	.	.	.	.	.	.	.	.	.	HCT (NS)
Ogura 2014 (TBSS)†[30]	MT	.	✓	.	✓	.	.	.	.	✓	.	.	✓	.	.	.	.	.	.	✓	.	.	.
Parimi 2016†[58]	MT	.	.	.	NR	NR	NR	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Paulus 2014†[26]	MT	.	.	✓	.	.	.	.	.	.	✓	.	.	.	.	.	.	.	.	.	.	.	.
Pezold 2012†[59]	MT	NS	.	.	NS	.	.	.	.	.	.	NS	.	.	✓	NS	.	.	✓	.	.	.	.
Plewa 2013[60]	MT	.	.	NR	.	.	.	..	.	.	.	.	.	.	.	.	.	.	.	.	.	.	Temp (NR) PRBC (NR)
Prichayudh 2014†[27]	SURG	.	.	✓	✓	✓	.	.	✓	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Rahbar 2015†[61]	MT	.	.	.	NS	✓	.	.	.	.	✓	NS	.	.	✓	.	.	.	.	.	.	.	Temp (NS)
Reisner 2016 [62]	MT	.	.	.	NR	NR	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	Smooth Muscle O2 (NR) Pulse Pressure (NR)
Salim 2008 [63]	EMB	✓	.	.	✓	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Schreiber 2007 [64]	MT	.	.	✓	.	.	.	..	.	.	✓	.	.	.	✓	.	.	.	.	.	.	.	.
Shackelford 2015 [65]	MT	.	.	.	NR	NR	.	.	.	.	.	.	NR	.	NR	.	.	.	.	.	.	.	Hct (NR) Glucose (NR) Potassium (NR) Chloride (NR) HC03 (NR) SpO2 Features (NR)
Sivrikoz 2014 [66]	SURG	.	.	✓	✓	✓	.	.	.	.	NS	.	.	.	.	.	.	.	.	.	.	.	.
Stanworth 2010†[67]	MT	.	✓	NS	✓	.	.	.	.	.	.	✓	.	.	.	.	.	.	.	.	.	.	Time to ED (NS)
Umemura 2016 [68]	MT	NR	.	.	NR	NR	.	.	.	NR	NR	✓	.	.	.	.	✓	.	.	NR	.	.	.
Vandromme 2010†[32]	MT	NR	NR	NR	.	.	.	.	.	.	.	.	✓	.	.	.	.	.	.	.	.	.	.
Vandromme 2011†[29]	MT	.	.	.	✓	✓	.	.	.	.	✓	.	✓	.	✓	.	.	.	.	.	.	.	.
Yucel 2006 (TASH)†[10]	MT	NR	.	.	NR	NR	.	.	.	NR	NR	NR	.	.	.	.	.	.	.	.	NR	.	.
Yumoto 2014 [69]	MT	.	.	.	.	.	.	.	.	.	.	NR	.	.	.	.	.	.	.	NR	.	.	.

Table 3 – Quality Assessment for Multivariable Prediction Models (N = 47)

Description – Outcome of Interest	**N (%)**
Massive Transfusion	37 (78.7%)
Embolization	2 (4.3%)
Surgery	3 (6.4%)
Two Outcomes	5 (10.6%)
Description –Primary Objective	
Evaluation of a Single Independent Predictor	21 (44.7%)
Development/Evaluation of Multivariable Prediction Model	26 (55.3%)
Quality Indicator – Clear Definition of Patient Population?	
Yes	47 (100%)
No	0 (0%)
Quality Indicator – Predictors Justified?	
Yes	15 (31.9%)
No	30 (63.8%)
Not Applicable (Studies Validating Existing Models Only)	2 (4.3%)
Quality Indicator – Clear Definition and Measurement of Predictors?	
Yes	32 (68.1%)
No	15 (31.9%)
Quality Indicator – Handling of Missing Data	
Excluded	13 (27.7%)
Multiple Imputation	1 (2.1%)
Unclear or Not Reported	33 (70.2%)
Quality Indicator – Variable Selection Strategy	
Significance on Bivariable Analysis	9 (19.1%)
Pre-Specified Clinical rationale	7 (14.9%)
Forward, Backward or Stepwise	19 (40.4%)
Unclear or Not Reported	10 (21.3%)
Not Applicable (Studies Validating Existing Models Only)	2 (4.3%)
Quality Indicator – Interactions Examined	
Yes	2 (4.3%)
Not Reported	43 (91.5%)
Not Applicable (Studies Validating Existing Models Only)	2 (4.3%)
Quality Indicator – Handling of Continuous Predictors	
Categorization	25 (53.2%)
Continuous (simple linear term)	12 (25.5%)
Not reported or unclear	2 (4.3%)
No Continuous Predictors Considered	8 (17.0%)
Quality Indicator – More than 10 Events Per Variable	
Yes	21 (44.7%)
No	16 (34.0%)
Unclear or Not Reported	8 (17.0%)
Not Applicable (Studies Validating Existing Models Only)	2 (4.3%)
Quality Indicator – Model Validation at Initial Study	
External Validation at Initial Study (Different Authors, Different Population)	4 (8.6%)
Internal Validation – Bootstrap Resampling	0 (0%)
Internal Validation – Split Sample (Same Authors, Same Population)	1 (2.1%)
Internal Validation – Split Sample (Same Authors, Different Population)	1 (2.1%)
Internal Validation – Temporal	4 (8.6%)
Internal Validation – Other	4 (8.6%)
No Validation	12 (25.5%)
Not Applicable – Evaluation of a Single Independent Predictor Only	21 (44.7%)
Quality Indicator – Model Presentation	
Equation	5 (10.6%)
Simplified Score	7 (14.9%)
Other	2 (4.3%)
Not Explained (Odds Ratios only – no Coefficients or Equation)	31 (66.0%)
Not Applicable (Studies Validating Existing Models Only)	2 (4.3%)

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Chapter 4 – National Survey of Canadian Traumatologists

This chapter incorporates the manuscript "A national survey of Canadian traumatologists' valuation of predictors for the identification of clinically significant bleeding in trauma patients". In accordance with the PROGRESS guidelines, this survey identifies candidate predictor variables of clinical importance for consideration of selection at the time of model pre-specification for the derivation study.

4.1 Predictors to Identify Clinically Significant Bleeding in Trauma Patients: A National Survey of Canadian Traumatologists

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Abstract:

Background: Rapid assessment and early intervention for traumatic hemorrhage reduces morbidity and mortality related to significant blood loss. However, there are no existing, well-validated approaches to identify high-risk patients. With the ultimate goal of deriving a clinical prediction rule for this purpose, we conducted a national survey of members of the Trauma Association of Canada to elicit their expert opinions about the relative importance of various candidate predictors for clinical assessment of traumatic hemorrhage.

Methods: A ten question electronic survey was distributed via email to all 153 staff physician members of the Trauma Association of Canada. In addition to querying respondent and institution demographics, the questionnaire asked respondents to rank ten candidate variables predicting the need for major intervention (surgery, embolization, massive transfusion) in bleeding trauma patients. Predictors were clinical, laboratory or imaging findings typically available within the first hour of trauma assessment.

Results: We received responses from 52 of 153 clinicians (34.0% response rate). The majority of respondents were Canadian (86.5%). The most common residency training programs completed were surgery (67.3%), emergency medicine (19.2%) and anesthesiology (3.9%). Hemodynamics was ranked within the top 5 predictors for all 52 respondents. Clinical examination, FAST, mechanism, blood gases and CT imaging consistently received top 5 ranks among more than half of respondents. In contrast, complete blood count, demographics and Glasgow Coma Scale placed within the top five most important predictors for well below 10% of respondents.

Conclusion: This national survey of traumatologists describes expert opinion on the relative importance of clinical, laboratory and imaging findings for the evaluation of traumatic hemorrhage. The classical clinical exam and valuation of hemodynamics remains the centerpiece

of this assessment although modernization of technology may explain the popularity of early imaging.

Level of Evidence: Epidemiologic/prognostic study, Level III

Background

Traumatic hemorrhage is responsible for nearly half of all mortality within the first 24 hours following an injury[1].The early mortality related to bleeding is especially pronounced within the first 6 to 12 hours and very few hemorrhagic deaths occur after the crucial first day[1, 2]. The early recognition of hemorrhage greatly influences the potential for aggressive, effective therapeutic interventions in order to improve outcomes and reduce mortality[3].

The Advanced Trauma Life Support (ATLS) guidelines describe a standardized approach to initial assessment and resuscitation of the trauma patient, including risk stratification strategies for classifying degree of hemorrhagic shock[4]. Despite their worldwide adoption, validation studies evaluating the ATLS classification of hemorrhage have demonstrated poor overall accuracy[4] and tend to overestimate the presence of hypotension and tachycardia in bleeding patients[5]. Considering these shortcomings, an international survey of ATLS course instructors demonstrated that only one in ten respondents believed the ATLS classification to be a "good guide for fluid resuscitation and blood product transfusion" [6].

Rapid assessment and risk stratification for identifying need for intervention in traumatic hemorrhage is of paramount importance to the traumatologist. As part of a larger project which aims to describe, understand and offer evidence-based refinement to this critical process through the development of a high quality clinical prediction rule, we conducted a national survey of Canadian traumatologists. This survey was an essential step which will be used, together with a systematic review[7], to inform the specification of a clinically relevant prediction model. To reduce the risk of over-fitting in building our clinical prediction model, we are adhering to recommendations by the Prognosis Research Strategy (PROGRESS) group, of pre-specification

based on the best available knowledge rather than a data-driven approach in which statistical significance testing is used to identify predictors[8].

Methods

We designed a simple, ten question survey reviewed and piloted by local trauma surgeons. The questionnaire included respondent demographics, institution characteristics, and respondent ranking of various predictors relating to hemorrhage assessment. Respondents were provided with a list of ten predictors comprised of clinical, laboratory and imaging variables based on findings from a recent systematic review[7] as well as determination by a local adjudication committee of trauma surgeons. Respondents were asked to rank their top five most important predictors when evaluating a patient for significant bleeding. Predictors include hemodynamics (systolic blood pressure, heart rate, and shock index), clinical exam suggestive of hemorrhage (visual confirmation of a bleeding wound or unstable pelvis), Focussed Abdominal Sonography for Trauma (FAST) examination, mechanism of injury, blood gases (base deficit, lactate, pH), computed tomography (CT) imaging (free fluid or contrast extravasation), coagulation studies (INR), complete blood count (hemoglobin, hematocrit), demographics (age, sex) and Glasgow Coma Scale (GCS). We tabulated rank lists and used a point system to create an overall ranking for each variable. For each respondent, a variable with a first place rank earned 5 points while a second place rank earned 4 points and so on. A variable that was unranked would not receive any points for that particular respondent.

Respondents were also asked to choose clinically important categorization thresholds for the continuous variables (systolic blood pressure, heart rate, shock index, hemoglobin, INR, lactate, pH and base deficit), based on perceived utility for inclusion into a clinical prediction rule. Although categorization of continuous predictors is not an efficient use of data and can lead

to bias[8], it is commonly used in prediction modeling to improve simplicity and acceptability of the resulting rule. Respondents were not provided with a free text option for identifying additional predictors.

The survey objectives and dissemination strategy were then peer-reviewed by clinical experts at the Trauma Association of Canada Annual Research Meeting in February 2017. The survey was electronically distributed via email by the Trauma Association of Canada to all 153 staff physician members in April 2017. Reminder emails were distributed at 2 and 4 weeks respectively. The survey was closed after 8 weeks. To preserve anonymity, identifying information was not collected, preventing a comparison of characteristics of respondents and non-respondents. Responses were collected via an electronic survey platform[9].The questionnaire is available from the corresponding author upon request. This study was approved by the Ottawa Health Sciences Network Research Ethics Board (OHSN-REB). As outlined in our cover letter to respondents, the return of the survey questionnaire was regarded as implied consent for study participation.

Results

Respondent and Institution Demographics

We received responses from 52 of 153 (34.0%) surveyed Trauma Association of Canada members. The respondent and institutional demographics are provided in Figure 1. The vast majority of respondents were Canadian (86.5%) but responses were also received from the United States (3.8%), Japan (1.9%), Philippines (1.9%), Qatar (1.9%), Saudi Arabia (1.9%), and Venezuela (1.9%). Most of the respondents (71.2%) worked at Level 1 equivalent trauma centers and were ATLS course instructors (76.9%). The most common residency training programs

completed were surgical (67.3%), emergency medicine (19.2%) and anesthesiology (3.9%). There was an almost even distribution among years of practice. Most respondents (65.4%) estimated institutional volumes of 1 – 10 patients per month requiring major intervention (hemostatic surgery, embolization, and massive transfusion) for traumatic hemorrhage.

Evaluation of Traumatic Hemorrhage

The compiled rankings of predictors are presented in Table 1. Patient hemodynamics earned 59.6% of the first rank votes while clinical exam followed with 32.0% of the first rank votes. FAST examination for free fluid, mechanism of injury, blood gases and CT imaging were regarded as the third to sixth most important predictors. Hemodynamics was ranked within the top 5 predictors for all 52 respondents. Clinical examination, FAST, mechanism, blood gases and CT imaging consistently received top 5 ranks among more than half of respondents. Conversely, complete blood count, demographics and GCS placed within the top 5 most important predictors for well below 10% of respondents.

Clinically Meaningful Categorization Thresholds

The preferred categorization thresholds for continuous variables are presented in Figure 2. For patient hemodynamics, the most commonly selected cut-point for systolic BP was less than 90 (57.7% of respondents). For coagulopathy, 65.4% of respondents preferred evaluating INR with a threshold of 1.5. For assessment of acid-base disturbance, 50% of respondents believed a base deficit threshold of 6 to be the most meaningful. Lastly, 61.5% of respondents believed classification of anemia as hemoglobin less than 90 to most appropriate.

Discussion

This national survey of Trauma Association of Canada members presents the first characterization of predictor valuation in traumatic hemorrhage evaluation to date. The most highly ranked components of the traumatic hemorrhage assessment remain the classical "circulation" aspect of the primary survey in terms of patient hemodynamics and obvious sources of bleeding. Current practice preferences appear to align well with recently validated massive transfusion prediction scores. All four predictors (penetrating mechanism, systolic BP, heart rate and FAST) comprising the ABC score[10] were ranked within the top five in our survey. Similarly, five of the eight predictors (unstable pelvis, FAST, heart rate, systolic BP, base excess) comprising the TASH score[3] are also ranked quite highly. Interestingly, this observation is coupled with what appears to be the modernization of the trauma assessment – an evolving appreciation for CT imaging, which ranked just outside the top five.

Rapid identification and management of exsanguinating hemorrhage remains a cornerstone of modern trauma care[11]. The latest edition of the European Guidelines on Management of Major Bleeding and Coagulopathy following Trauma advocates for minimization between injury time and bleeding control as well as a holistic approach to traumatic hemorrhage assessment[12]. Although clinical judgment is indeed fallible and there certainly exist a need for evidence-based approaches to traumatic hemorrhage evaluation[13], there remains great value in surveying the existing landscape in order to assess the clinical practice adoption of existing literature or guidelines.

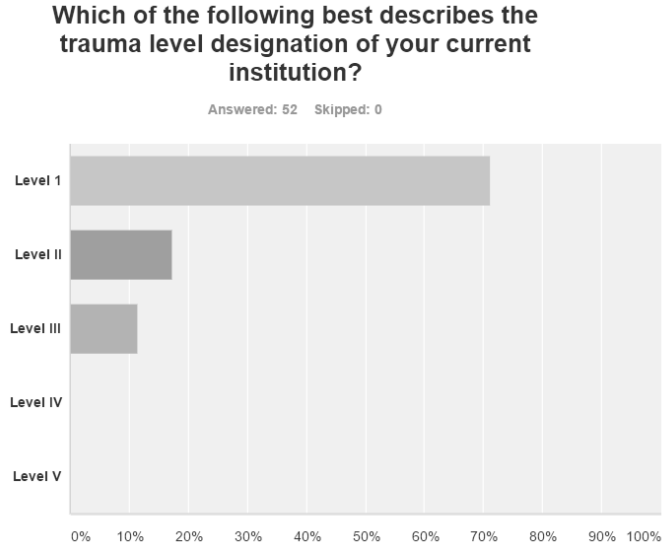
Our findings should be interpreted with the following considerations of limitations. Our survey was limited to primarily Canadian traumatologists functioning in a health care system

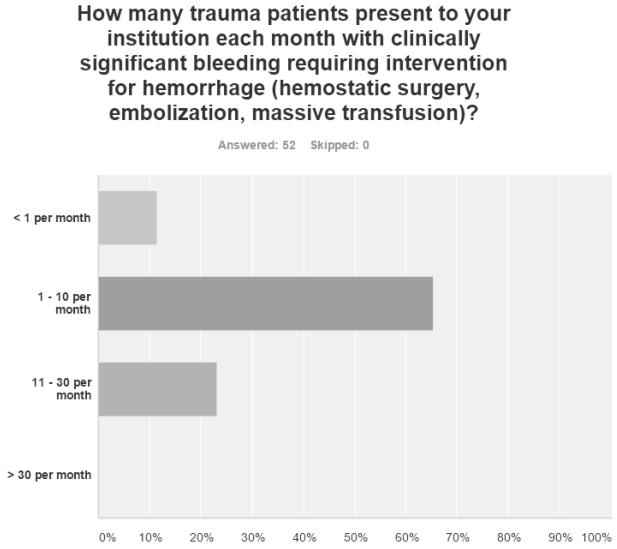
with regionalized trauma services. The vast majority of major traumas at risk for clinically significant hemorrhage are readily transferred to tertiary care trauma centres with more specialized expertise and technological resources[14]. In addition, the relative paucity of firearms in Canada skews toward a significantly lower proportion of penetrating trauma as compared to the United States[1, 15], which may predispose toward a higher prevalence of imaging for diagnostic evaluation of blunt injury. Lastly, while our response rate compares favorably to other reported specialist response rates to web-based surveys[16], we acknowledge the potential for selection bias and random error associated with our results.

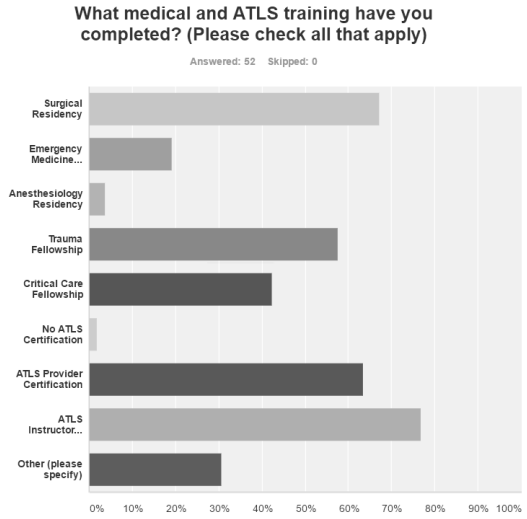
Conclusion

This national survey of Canadian Trauma Association traumatologists describes the relative importance of predictors for evaluation of traumatic hemorrhage based on expert opinion of practitioners. The classical clinical exam and valuation of hemodynamics remains the centerpiece of this assessment although modernization of technology may explain the popularity of early imaging. The results from this survey will be used to inform the derivation of a high quality clinical prediction rule to identify clinically significant bleeding in trauma patients.

Figure 1 – Respondent and Institution Demographics







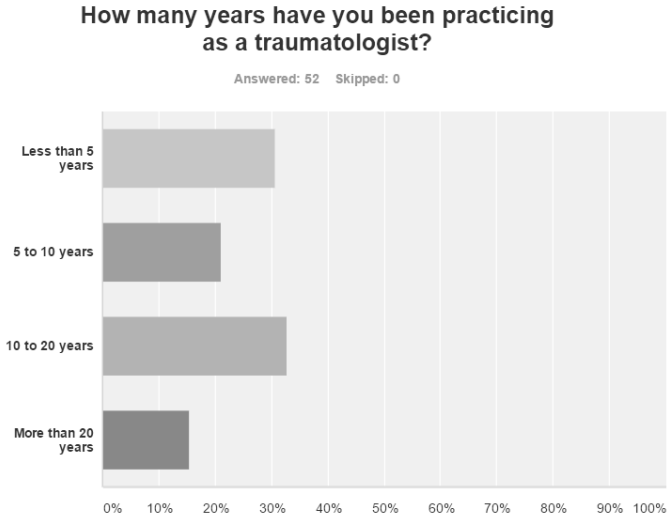
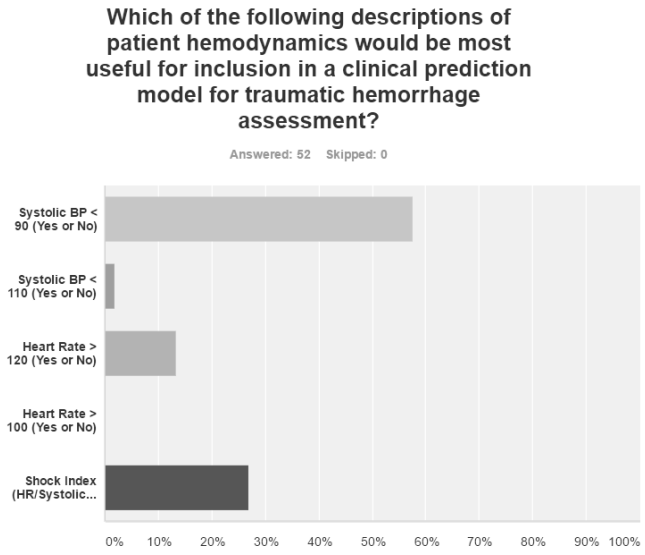
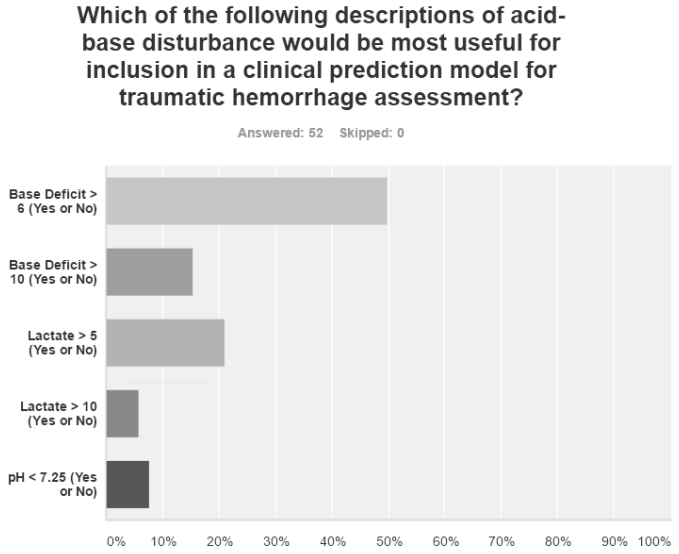
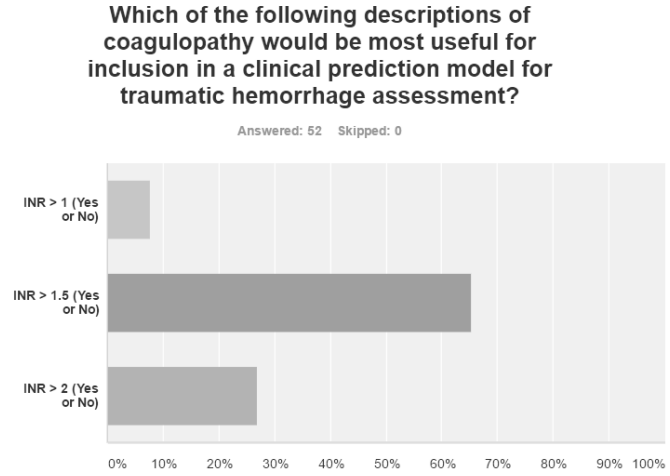


Figure 2 – Categorization Thresholds







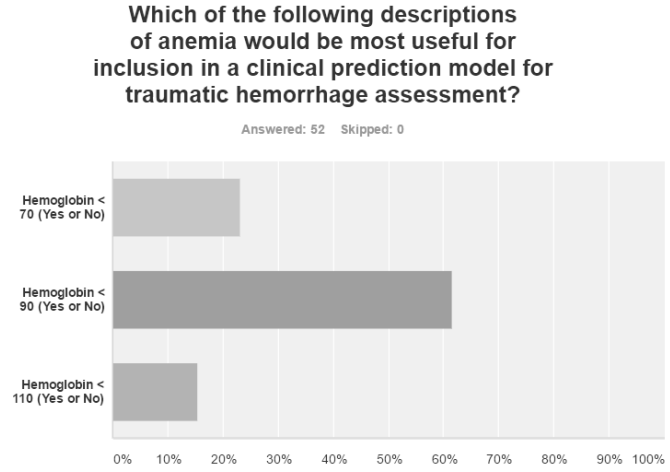


Table 1 - Clinical Expert Ranking of Predictor Variables for Traumatic Hemorrhage Evaluation

Predictors	1st rank votes	2nd rank votes	3rd rank votes	4th rank votes	5th rank votes	Total Score	Total Number of Top 5 Ranks
Hemodynamics	31	15	4	1	1	230	52
Clinical Exam (Bleeding Wound or Unstable Pelvis)	16	20	9	4	1	196	50
FAST	0	6	16	16	7	111	46
Mechanism	5	5	11	11	3	103	35
Blood Gases (BD, Lactate, pH)	0	4	6	7	16	64	33
CT Imaging	0	2	4	8	15	51	29
Coagulation (INR, aPTT)	0	0	0	2	5	9	7
CBC (Hgb, Hct)	0	0	2	1	0	8	3
Demographics	0	0	0	1	3	5	4
Glasgow Coma Scale	0	0	0	1	1	3	2

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Chapter 5 – Derivation and Internal Validation of a Clinical Prediction Model

This chapter incorporates the manuscript “Early identification of the need for major intervention in patients with traumatic hemorrhage: development and internal validation of the Canadian Bleeding (CAN-BLEED) score”. A model is pre-specified based on findings from the previously discussed systematic review and survey studies and assessed within the context of a cohort from the Ottawa Hospital. This prediction model derivation study is the ultimate focus and culmination of this thesis work.

5.1 Early Identification of the Need for Major Intervention in Patients with Traumatic Hemorrhage: Development and Internal Validation of the Canadian Bleeding (CAN-BLEED) Score

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Abstract

Background: Uncontrolled bleeding is the most common cause of preventable death following a traumatic injury. Failure to rapidly identify the source and extent of bleeding results in worsening coagulopathy and increased morbidity as a consequence of the low perfusion state. The existing clinical aids for risk stratification of bleeding patients account only for massive transfusion, a concept limited by survivorship and competing risk bias. An evidence-based tool for identifying bleeding patients requiring escalation of care beyond initial resuscitation is needed.

Methods: We included all patients presenting with major blunt or penetrating trauma, defined as ISS > 12 or requiring trauma team activation, to the Ottawa Hospital from September 2014 to February 2017. The primary outcome of interest was a composite comprised of the need for massive transfusion, embolization or surgery for hemostasis. Predictors considered were clinical, laboratory or imaging findings available within the first hour of assessment. In accordance with the methodology outlined by the Prognosis Research Strategy Guidelines, we derived the rule using a logistic regression model based on the pre-specification of predictors from the best available clinical knowledge and literature. Findings from a previously conducted systematic review and survey of Canadian traumatologists were used by an adjudication committee to inform variable selection. We used multiple imputation to account for missing data and modelled continuous predictors using restricted cubic splines. A stepdown procedure was used to simplify the model while retaining maximal prognostic value. Model performance was assessed using a receiver-operating curve and the optimism was determined using internal bootstrap validation. Weighted regression coefficients were used to calculate a five variable score for bedside

application. The model was additionally assessed for discrimination, calibration and sensitivity and specificity at specific cutpoints.

Results: We included 748 patients including 110 requiring a major intervention. Based on the findings of these two studies, the predictors selected for pre-specification by the adjudication committee were systolic blood pressure, heart rate, clinical exam suggestive of bleeding, CT imaging, FAST ultrasound, lactate and hemoglobin. Following stepdown, the final multivariable model was comprised of five variables: systolic blood pressure, clinical exam suggestive of hemorrhage, lactate, FAST ultrasound and CT imaging. The naive c-statistic for the model was 0.953 (0.952 following optimism-correction). These five variables were converted to a simple score, termed the Canadian Bleeding (CAN-BLEED) score.

Conclusion: A simple Canadian Bleeding Score is proposed based on five variables in order to systematically identify high risk patients requiring major intervention for traumatic bleeding. Multi-centre derivation and external validation studies are required prior to implementation.

Background

Exsanguination is the second leading cause of mortality following a traumatic injury, and is responsible for nearly half of all deaths within the first 24 hours [1, 2]. Uncontrolled bleeding is the most common cause of preventable mortality following both military and civilian trauma [3]. Delay in recognizing significant bleeding results in larger blood volume losses, higher resuscitation requirements, and severe physiologic derangements [2]. Major interventions to address ongoing hemorrhage may include massive transfusion, hemostatic surgery or angioembolization. The early identification of hemorrhagic injury is a critical component of modern trauma care [4] and an objective, evidence-based approach to bleeding assessment would be invaluable for triage decisions and provision of lifesaving interventions [3].

The widely adopted 9th edition of the Advanced Trauma Life Support (ATLS) guidelines provide an algorithmic approach to initial assessment of the trauma patient including a four-class system for grading severity and proposed corresponding management of hemorrhage based on clinical examination and disturbances in baseline vital signs [5]. However, several studies evaluating the ATLS classification in recent years have raised concerns regarding its reliability and usefulness. A large database validation of the Trauma Audit and Research Network in the United Kingdom showed that the ATLS guidelines significantly overestimated the degree of tachycardia and hypotension associated with blood loss [6]. Similarly, another multi-centre validation effort by the Trauma Registry of the German Society for Trauma Surgery demonstrated that fewer than 1 in 10 patients could be accurately classified according to the ATLS system [5]. In other words, significant hemorrhage often occurs insidiously before obvious disturbances in vital signs may appear. In a recent international survey, only 10.9% of

ATLS course directors and instructors considered the ATLS classification of hemorrhagic shock to be a “good guide for fluid resuscitation and blood product transfusion” [7].

A recent national survey of Canadian traumatologists demonstrated that, while clinicians value measures of patient hemodynamics such as blood pressure or heart rate, they preferred a holistic approach to hemorrhage assessment in their current practice, incorporating clinical exam, bloodwork, bedside Focussed Abdominal Sonography for Trauma (FAST) and Computed Tomography (CT) imaging [8]. Despite an abundance of available diagnostic tests, clinical gestalt for identification of bleeding trauma patients requiring major intervention continues to perform quite poorly demonstrating 65.6% sensitivity, 63.8% specificity and c-statistic of 0.63.[9]. Recognizing the fallibility of clinical judgment and the need for validated, objective approaches to traumatic hemorrhage prognostication [3], the trauma community has witnessed the growing popularity of clinical prediction models over the last few years [10]. However, the methodological quality of the traumatic hemorrhage prediction literature has generally failed to meet expert guideline recommended standards for development and validation [10]. In addition, the vast majority of existing modeling studies focus on massive transfusion as a sole outcome of interest, a concept shown to be vulnerable to competing risk bias and survivorship bias [11, 12].

While some patients arrive to hospital with obvious evidence of significant blood loss and clear indication for urgent intervention, there remains a subset of the trauma population for whom the classical clinical and biochemical signs of hemorrhage may not be as readily apparent. In this study, we sought to develop and internally validate a clinical prediction model capable of identifying the need for major intervention in patients with traumatic hemorrhage early into the initial clinical assessment.

Methods

Population

This cohort study is based on data obtained from the Ottawa Trauma Registry, a prospectively collected database for the Ottawa Hospital, over the period of September 2014 to February 2017. The Ottawa Hospital is the designated Level 1 trauma center for the Champlain Local Health integration Network (LHIN) in Eastern Ontario. Inclusion into the database requires a classification as a major trauma, defined as injury severity score (ISS) > 12 or requiring trauma team activation, a standardized definition utilized across the province of Ontario. We included all patients arriving alive directly from the trauma scene or transferred to the study hospital from another receiving hospital within 3 hours of injury, excluding patients with a delayed presentation or those that were dead on arrival. We included blunt or penetrating mechanisms of injury only, excluding non-hemorrhagic mechanisms such as burn injury, drowning, strangulation, and electrocution. We excluded patients with isolated head injury, defined as Abbreviated Injury Scale (AIS) score > 2 for head injury without concomitant injury of the thorax, abdomen or pelvis. This study was reviewed and approved by the Ottawa Health Science Network Review Ethics Board.

Outcome Measures

The primary outcome is the occurrence of clinically significant bleeding requiring corrective intervention(s) within the first 24 hours of presentation to hospital, defined as a composite of the following interventions: massive transfusion (≥ 10 units packed red cells), surgery for hemostasis, or angiography with embolization. To correctly classify surgical outcomes, we reviewed all operative reports for eligible patients and included those requiring

thoracotomy, laparotomy, pelvic fixation, or vascular surgery with a hemostatic intervention. Patients receiving an exploratory operation without confirmation of a therapeutic hemostatic procedure within the operative report were classified as non-events. Hemostatic procedures include packing for hemostasis, ligation of bleeding vessels or removal of bleeding organs. Patients receiving angiography without embolization as described within the diagnostic imaging report were similarly classified as non-events. Time from initial arrival in the Emergency Department (ED) to occurrence of first major intervention was calculated for all outcomes. Massive transfusion, as assessed by blood product administration records, was considered to have occurred upon the initiation of the 10^{th} unit of packed red cells.

Analysis Plan

The analysis protocol was designed in accordance with the recommendations provided by Harrell [13] and Steyerberg [14] for the development of a clinical prediction model using logistic regression. We prioritized full pre-specification of the predictor variables, use of flexible functions for continuous predictors, and avoidance of data-driven methodology for predictor selection. All analyses were conducted using Harrell's Hmisc package [15] in R 3.3 and SAS 9.4 software [16].

Model Pre-Specification

We aimed to utilize the best available knowledge to facilitate pre-specifying predictors for the model. Model pre-specification, based on clinical knowledge and previous studies, minimizes over-reliance on small datasets and improves the model's performance at external validation [14]. We first conducted a systematic review in order to identify important predictors in the existing literature [10, 17]. We then conducted a national survey of Canadian

traumatologists [8] and asked respondents to rank order various predictors in terms of clinical importance when evaluating a trauma patient's risk for bleeding. Utilizing an adjudication committee based on a convenience sample of local trauma surgeons, we reviewed the results of the systematic review and national survey and selected the most appropriate predictors for our pre-specified model.

Data Coding, Missing Values and Multicollinearity

All data collection was completed by a single reviewer (AT). Extraction of predictors was not blinded to outcome. The data extraction form was pilot-tested and data were extracted according to a pre-specified protocol. From an exploratory analysis of missing data, we identified four variables with >25% prevalence of missing values: FAST, pH, lactate and base excess. Following consultation with clinical experts in trauma and laboratory medicine, it was determined that missing values on these variables are likely to result from low risk patients who have values within a normal clinical range. Therefore, for modeling purposes, we categorized these variables as either abnormal or not, using pre-specified thresholds of known clinical importance with all missing values assumed to be normal. FAST performed and positive, pH < 7.25 lactate >5 and base excess < -6 were considered abnormal findings. The appropriateness of this assumption was investigated by comparison with imputed values generated under a multivariable imputation model. All remaining continuous variables were modelled using restricted cubic splines. We used a multiple imputation technique to impute missing values on predictor variables using the aregImpute function in the Hmisc library [13]. This procedure simultaneously imputes missing variables while determining optimal transformations among all imputation variables. The imputation model consisted of the full list of predictor variables, outcomes, and available ancillary variables (such as age, sex, and time to hospital). Variance

Inflation Factors (VIFs) were used to examine multi-collinearity and variables involved in collinear relationships were excluded based on clinical importance.

Degree of Freedom Allocation

Based on the available number of events and a commonly used rule of 10 events per predictor, our adjudication committee pre-specified a model based on the available 11 degrees of freedom (df). Three knots (two df) were considered adequate to capture clinically relevant associations for continuous predictors. The predictors comprising the full model are provided in Appendix 1.

Model Derivation

An initial main effects model was fit using logistic regression with continuous predictors modelled using restricted cubic splines. Final degree of freedom allocation was determined based on importance of each predictor using a partial Chi-squared test of association with the outcome such that variables with higher predictive potential were allocated more degrees of freedom. This process of specification does not increase the type II error as predictors are retained in the full model irrespective of the strength of association.

Model Performance and Internal Validation

Model performance was assessed by the concordance index (c-statistic). During model development for outcome prediction, the primary objective is naturally to provide predictions that would be valid in new populations. However, there is the potential for overfitting where the model describes the derivation population well, but struggles to provide accurate predictions for new subjects [14]. In other words, overfitting causes overly optimistic expectations of the

model's performance in external populations. Internal validation using 1000 bootstrap samples was used to quantify this optimism and to provide an adjusted evaluation of performance that could be expected during external validation. Model calibration was assessed using the Hosmer-Lemeshow test and calibration plots which compared the observed and predicted probabilities within deciles of predicted risk. We assessed model discrimination using box plots in order to ensure appropriate separation of groups with and without the outcome of interest.

Model Simplification

We evaluated the model using the stepdown approach described by Harrell [15], setting a rule for selection based on the Akaike information criterion (AIC). A simplified score was calculated by dividing the weighted estimated coefficients to obtain the lowest whole integers. Categorization of systolic BP was performed at this stage for presentation in the format of a score. We used a receiver operative curve analysis to assess sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the curve for the simplified score as compared to the full complex model.

Results

A total of 748 patients were included in the study, of which 110 required at least one of the three pre-determined composite outcomes representing major intervention for hemorrhage. Patient demographics, baseline characteristics and outcomes are presented in Table 1. The most common mechanism of injury was high velocity blunt injury (64.0%). There were 148 (19.8%) patients transferred from peripheral hospitals with a median (Q1 – Q3) transfer time of 1.0 (0.5 – 2.0) hours. FAST was performed in 469 (62.7%) of which 74 (15.8%) were positive. CT imaging was performed in 662 (88.5%) of which 181 (27.4%) demonstrated free fluid and 60 (9.1%)

demonstrated contrast extravasation. There were 46 (6.1%) patients requiring only hemostatic surgery, 18 (2.4%) patients requiring only embolization and 5 (0.7%) patients requiring only massive transfusion while the remaining 41 (5.5%) patients required two or more major interventions. Twelve (1.6%) patients died from hemorrhage within the first 24 hours. Prevalence of missing data was less than 25% for all variables. We used the generated values from multiple imputation for the four re-categorized variables (FAST, lactate, pH and base excess) and demonstrated that >85% of these values for each variable would indeed have been classified as “negative for significant abnormality", thus providing support for the deterministic imputation of these values as being within normal range.

The full pre-specified model prior to the stepdown procedure is presented in Appendix 1. After application of the stepdown procedure, the final multivariable model, presented in Table 2, includes clinical examination suggestive of hemorrhage (odds ratio 4.58, 95% CI 2.25 – 9.35), FAST (odds ratio 2.67, 95% CI 1.28 – 5.58), lactate > 5 (odds ratio 3.44, 95% CI 1.43 – 8.29), free fluid or contrast extravasation on CT (odds ratio 22.20, 95% CI 8.51 – 57.91) and systolic blood pressure. Blood pressure is represented by a cubic spline function with 3 knots. For ease of interpretation, a comparison for patients with 80 vs. 120 mmHg, based on clinically important thresholds, demonstrates an odds ratio 4.58, 95% CI 2.25 – 9.35.

Goodness of fit testing of the simplified model is presented in Table 3, organized by decile of predicted risk. In each decile, we present the expected probability, expected number of events, observed probability and observed number of events. There were no statistically significant differences between observed and predicted number of events for any risk decile. A Hosmer-Lemeshow test for overall model fit yielded a p-value = 0.83, which demonstrates good

model fitting. The naïve c-statistic for the simplified model was 0.953 whereas the optimism-corrected c-statistic was 0.952, demonstrating that there was little optimism in the model.

Utilizing the weighted estimation coefficients, we calculated a simplified prediction score, presented in Table 4. Clinically meaningful categorization thresholds of 90 and 120 mmHg were chosen for systolic BP, based on the results of a previous survey [8]. The remaining categorical variables are denoted as simple yes or no answers. The maximum overall score is maintained at 10 points for ease of use.

The simplified score was compared to the final multivariable model using an ROC curve analysis, presented in Figure 1. The simplified score demonstrated a c-statistic = 0.952 (95% CI 0.934 – 0.971) as compared to c = 0.953 (0.933 – 0.974) for the full model, suggesting that that the simplified score was no worse than the complex model. Comparison between the two ROC functions based on AIC yielded no significant difference (p = 0.75).

Classification performance for the simplified score is presented in Table 5, organized by incremental cut-offs of 0.5 points. At a score cut-off of 3 points or greater, the simplified score demonstrates 98.2% (95% CI 93.6 to 99.8) sensitivity, 79.2% (95% CI 76.0 to 82.3) specificity, 44.8% (95% CI 38.5 to 51.1) positive predictive value and 99.6% (95% CI 98.5 to 100) negative predictive value.

The time to first major intervention is presented in Table 6. The median (Q1 – Q3) time to first major intervention for all 110 patients was 2.0 (1.0 – 4.0) hours. Of these patients, 40 (36.4%) received their first intervention > 3 hours after arrival to ED, 16 (14.5%) after > 6 hours, and 6 (5.4%) after > 12 hours. The patients requiring only hemostatic surgery were generally the quickest to receive an intervention, with a median (Q1 – Q3) time of 1.5 (0.63 – 3.0) hours. In

contrast, patients receiving only embolization were the slowest to receive an intervention, with a median (Q1 – Q3) time of 5.3 (4.0 – 6.4) hours.

Noting the potential for competing risk and survivorship bias, we conducted a sensitivity analysis with a four-outcome composite that additionally included death from hemorrhagic causes within 24 hours. However, there was no significant change to the final model composition.

Discussion

In this study, we developed and internally validated the Canadian Bleeding (CAN-BLEED) score for early identification of patients requiring major intervention for traumatic hemorrhage. In accordance with the methodology described by the PROGRESS guidelines [18] and methodological experts [13, 14], we pre-specified a full clinical prediction model based on the best available clinical expertise and literature. The complex model was then simplified to an easy to calculate score for pragmatic bedside application. The simplified score was comprised of five predictors, typically available to the clinician during the first hour of trauma resuscitation: systolic BP, clinical exam, FAST, lactate and CT findings. Evaluation of the score demonstrated excellent overall performance (c = 0.952) with a cut-off of 3 points or greater yielding both high sensitivity and specificity. Perhaps most importantly, the score cut-off of 3 points functioned exceptionally well as a potential screening tool, demonstrating a negative predictive value of 99.6% for ruling out impending need for major intervention. Lastly, overfitted models tend to underestimate event probability in low risk patients and overestimate event probability in high risk patients [19]. In this cohort, we demonstrated excellent fitting of observed vs. predicted

probabilities across all grouped deciles of risk, which suggests that the score performs well for both high and low risk patients.

Despite well-established principles emphasizing minimization of time to bleeding control and resuscitation [20], challenges remain in terms of accurately identifying or ruling out hemorrhagic shock [3]. In a study of hemorrhage following blunt abdominal trauma, there were delays in identifying and treating the major source of injury in 24% of cases, most commonly due to insidious pelvic bleeding [4]. In our own population, we note that 36.4% of patients requiring major intervention received their treatment more than 3 hours after initial presentation, and 14.5% of patients waited more than 6 hours. These considerations clearly present an opportunity for improvement in the appropriate risk stratification of patients and potential reduction of time to intervention.

Our proposed score shares many of the same elements as the previously developed ABC and TASH scores for prediction of massive transfusion, notably the systolic blood pressure [21, 22], FAST ultrasound [21, 22] and pelvic instability [22]. Most of the remaining variables such as mechanism of injury [21], heart rate [21, 22], hemoglobin [22] and base excess [22] were additionally included within the pre-specified model but removed during stepdown procedure as they did not contribute significant prognostic information. Of note, the five components (clinical exam, systolic BP, lactate, FAST and CT) of our proposed score all received Grade 1 recommendations by the European Guidelines on Management of Major Bleeding for inclusion within the standard assessment for hemorrhage [20].

Strengths of this study include the rigorous adherence to prediction modeling methodology standards, in particular the comprehensive process of model pre-specification

utilizing the best available literature and clinical expertise. In addition, we sought to maintain practicality and clinical functionality during model development, incorporating clinical expertise for determination of model composition and categorization thresholds. Lastly, the adoption of a score based entirely on predictors typically available within the first hour offers the potential for earlier identification of high risk patients and reduction of time to intervention.

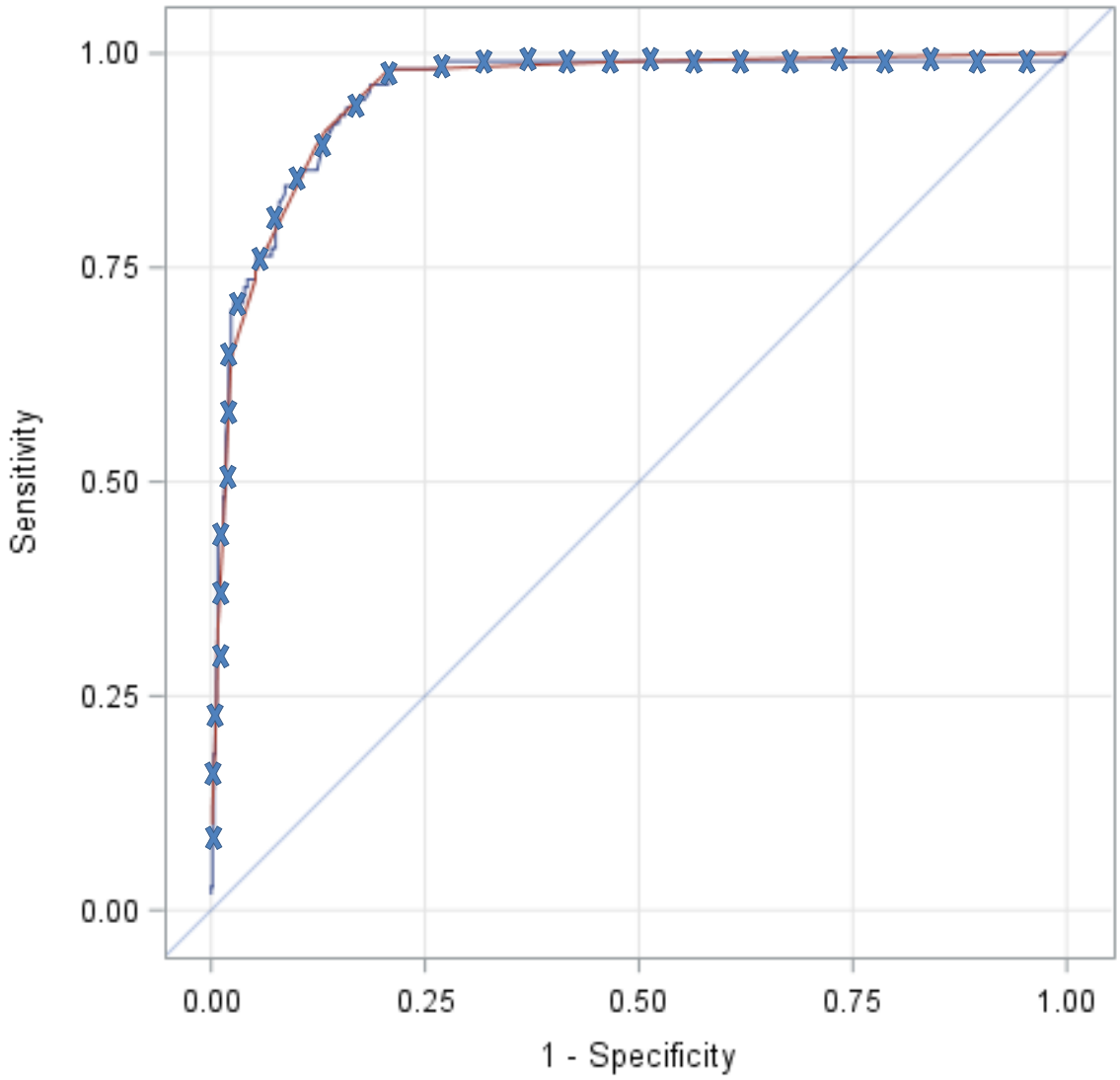
We note the following limitations for consideration. Our model development is based on a Canadian tertiary care centre with specialized expertise and resources, functioning in a healthcare system with regionalized trauma services [23]. We recognize that smaller community hospitals may not have readily available access to CT imaging, which comprises an important predictor in our score. However, we note that obtaining a score of 3 points or greater based on the remaining four widely available variables (systolic BP, clinical exam, FAST, lactate) may serve as a useful screening tool to identify those benefiting from transfer to major trauma centres, particularly since these patients are likely to require specialized interventions (hemostatic surgery, embolization, massive transfusion) typically not available in hospitals without trauma services. In addition, we acknowledge that interpretations of pelvic stability, visualization of active bleeding as well as FAST and CT imaging may be subject to variable inter-rater reliability. However, our pragmatic approach to data collection based on the documented findings presented by the radiologists' report and traumatologist consultant note rather than single reviewer re-interpretation of primary data, accounts for subjective decision making across multiple clinicians of varying expertise and levels of training. Lastly, while pre-specified models with appropriate bootstrap correction for optimism typically perform well in external validation, the evaluation of the score in different populations and settings remains an important step before widespread adoption [14]. Given the limitations including involvement of a single center, use of

retrospectively collected data, modest sample size and required re-categorization of missing variables, this dataset will serve as a preliminary derivation study. A Canadian multicentre derivation study to further refine and validate this score is planned.

Conclusion

In summary, this study adopted robust methodology for clinical prediction modeling and synthesised the best available clinical and evidence-based knowledge to develop and internally validate the Canadian Bleeding (CAN-BLEED) score for early identification of patients requiring major intervention following traumatic hemorrhage. A simple, five variable score is proposed based on predictors available to the clinician within the first hour of assessment: systolic BP, clinical exam, FAST, lactate and CT imaging. The score demonstrates excellent sensitivity and specificity, offering considerable promise as a screening tool for early risk stratification of bleeding trauma patients. Multicentre studies are required to further refine the score, confirm adequate performance, inter-rater reliability and potential for reduction of time to intervention.

Figure 1 – Receiver Operating Curve Comparison for Final Model vs. Simplified Score



Final Model	0.953 (95% CI 0.933 – 0.974)
Simplified Score	0.952 (95% CI 0.934 – 0.971)
Comparison (AIC)	P = 0.75

Table 1 – Patient Demographics, Baseline Characteristics & Outcomes

Total Number of Patients	N = 748
Patient & Injury Demographics	
Age (Years)	43.0 (26.0 – 5.9.0)
Sex (Male)	560 (74.9%)
Mechanism	
High Velocity Blunt	479 (64.0%)
Low Velocity Penetrating	130 (17.4%)
Low Velocity Blunt	103 (13.8%)
High Velocity Penetrating	36 (4.8%)
Injury Severity Score (ISS)	17.0 (12.0 – 25.0)
Transferred From Another Hospital	148 (19.8%)
Time To Hospital (Hours)	1.0 (0.5 – 2.0)
Baseline Clinical Characteristics	
Initial Systolic Blood Pressure in ED	125.0 (110.0 – 140.0)
Initial Heart Rate in ED	92.0 (78.0 – 109.0)
Glasgow Coma Scale (GCS)	15.0 (14.0 – 15.0)
Clinical Pelvic Instability	32 (4.3%)
Visualization of Actively Bleeding Wound	34 (4.7%)
Focussed Abdominal Sonography (FAST) Performed	469 (62.7%)
FAST Positive	74 (15.8%)
Hemoglobin	138.0 (124.0 – 150.0)
International Normalized Ratio (INR)	1.1 (1.0 – 1.2)
pH	7.31 (7.23 – 7.36)
Base Excess	-2.50 (-5.5 – 0.3)
Lactate	3.0 (2.3 – 4.7)
Computed Tomography (CT) Imaging Performed	662 (88.5%)
Free Fluid on CT	181 (27.4%)
Contrast Extravasation on CT	60 (9.1%)
Outcomes	
Any Major Intervention	110 (14.7%)
Surgery Only	46 (6.1%)
Embolization Only	18 (2.4%)
Massive Transfusion Only	5 (0.7%)
Two or More Major Interventions	41 (5.5%)
Death from Hemorrhage within 24 Hours	12 (1.6%)

Categorical values presented as n (%); Continuous variables presented as median (Q1 – Q3)

Table 2 – Final Multivariable Model

Variable	Odds Ratio	Coefficient	Standard Error	P – Value
Intercept	-	1.12	1.21	0.93
Systolic BP (80 vs. 120 mmHg)	4.58 (2.25, 9.35)	-	-	-
Systolic BP	-	-0.04	0.01	<0.0001
Systolic BP*	-	0.03	0.02	0.03
Clinical Exam Suggestive of Hemorrhage (Clinical Pelvic Instability or Visualization of Active Bleeding)	15.75 (6.30, 39.37)	2.76	0.47	<0.0001
FAST Positive	2.67 (1.28, 5.58)	0.98	0.38	0.01
Lactate > 5	3.44 (1.43, 8.29)	1.24	0.45	0.01
Free Fluid or Contrast Extravasation on Computed Tomography (CT)	22.20 (8.51, 57.91)	3.10	0.49	<0.0001

Systolic BP represented as cubic spine function with 3 knots; odds ratio is presented based on comparison 80 vs. 120 mmHg

Table 3 – Goodness of Fit Testing

Decile	N	Expected Probability	Expected # of Events	Observed proportion of events	Observed # of Events	P-Value
1st to 10th percentile	76	0.70%	0.53	1.32%	1	0.52
11th to 20th percentile	74	0.71%	0.53	0%	0	0.47
21st to 30th percentile	78	0.75%	0.58	0%	0	0.44
31st to 40th percentile	78	0.80%	0.62	0%	0	0.43
41st to 50th percentile	69	0.88%	0.61	0%	0	0.43
51st to 60th percentile	75	1.2%	0.87	0%	0	0.35
61st to 70th percentile	74	5.3%	3.91	8.10%	6	0.28
71st to 80th percentile	75	14.3%	10.72	14.7%	11	0.93
81st to 90th percentile	75	36.9%	27.64	38.7%	29	0.75
91st to 99th percentile	74	86.5%	63.99	85.1%	63	0.74

Overall Hosmer-Lemeshow Test: Chi Square 5.05, p-value = 0.83 (suggests good fit)

Table 4 – Canadian Bleeding (CAN-BLEED) Score

Variable	**Points**
Systolic Blood Pressure	
<90 mmHg	2.5
90 – 120 mmHg	1
> 120 mmHg	0
Clinical Exam (Pelvic Instability of Visualization of Active Bleeding)	
Yes	2.5
No	0
FAST	
Positive	1
Negative	0
Lactate > 5	
Yes	1
No	0
Free Fluid or Contrast Extravasation on Computed Tomography (CT)	
Yes	3
No	0
Total Score	10

Table 5 – Classification Table for the CAN-BLEED Score

Score Cut-offs	Predicted Probability at Score	Test Positive	Test Negative	True Positive	False Positive	True Negative	False Negative	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
0	0.6%	748	0	110	638	0	0	100 (99.5 to 100)	0%	14.7 (12.2 to 17.2)	N/A
0.5	1.0%	426	322	109	317	321	1	99.1 (95.0 to 100)	50.3 (46.4 to 54.2)	25.6 (21.4 to 29.7)	99.7 (98.3 to 100)
1	1.6%	426	322	109	317	321	1	99.1 (95.0 to 100)	50.3 (46.4 to 54.2)	25.6 (21.4 to 29.7)	99.7 (98.3 to 100)
1.5	2.6%	268	480	108	160	478	2	98.2 (93.6 to 99.8)	74.9 (71.6 to 78.3)	40.3 (34.4 to 46.2)	99.6 (98.5 to 100)
2	4.1%	268	480	108	160	478	2	98.2 (93.6 to 99.8)	74.9 (71.6 to 78.3)	40.3 (34.4 to 46.2)	99.6 (98.5 to 100)
2.5	6.5%	252	496	108	144	494	2	98.2 (93.6 to 99.8)	77.4 (74.2 to 80.7)	42.9 (36.8 to 49.0)	99.6 (98.5 to 100)
3	10.3%	241	507	108	133	505	2	98.2 (93.6 to 99.8)	79.2 (76.0 to 82.3)	44.8 (38.5 to 51.1)	99.6 (98.5 to 100)
3.5	15.7%	185	563	100	85	553	10	90.9 (85.5 to 96.3)	86.7 (84.0 to 89.3)	54.1(46.9 to 61.2)	98.2 (97.1 to 99.3)
4	23.4%	176	572	98	78	560	12	89.1 (83.3 to 94.9)	87.8 (85.2 to 90.3)	55.7 (48.3 to 63.0)	97.9 (96.7 to 99.1)
4.5	33.3%	115	633	82	33	605	28	74.6 (66.4 to 82.7)	94.8 (93.1 to 96.6)	71.3 (63.0 to 79.6)	95.6 (94.0 to 97.2)
5	44.9%	114	634	81	33	605	29	73.6 (65.4 to 81.9)	94.8 (93.1 to 96.6)	71.1 (62.7 to 79.4)	95.4 (93.8 to 97.1)
5.5	57.1%	86	662	71	15	623	39	64.6 (55.6 to 73.5)	97.7 (96.5 to 98.8)	82.6 (74.5 to 90.6)	94.1 (92.3 to 95.9)
6	68.5%	68	680	57	11	627	53	51.8 (42.5 to 61.2)	98.3 (97.3 to 99.3)	83.8 (75.1 to 92.6)	92.2 (90.2 to 94.2)
6.5	78.1%	67	681	56	11	627	54	50.9 (41.6 to 60.3)	98.3 (97.3 to 99.3)	83.6 (74.7 to 92.5)	92.1 (90.0 to 94.1)
7	85.3%	41	707	36	5	633	74	32.7 (24.0 to 41.5)	99.2 (98.5 to 99.9)	87.8 (77.8 to 97.8)	89.5 (87.3 to 91.8)
7.5	90.5%	41	707	36	5	633	74	32.7 (24.0 to 41.5)	99.2 (98.5 to 99.9)	87.8 (77.8 to 97.8)	89.5 (87.3 to 91.8)
8	94.0%	30	718	26	4	634	84	23.6 (15.7 to 31.6)	99.4 (98.4 to 99.8)	86.7 (69.3 to 96.2)	88.3 (86.0 to 90.7)
8.5	96.2%	14	734	13	1	637	97	11.8 (5.8 to 17.9)	99.8 (99.1 to 100)	92.9 (66.1 to 99.8)	86.8 (84.3 to 89.2)
9	97.6%	12	736	11	1	637	99	10.0 (4.4 to 15.6)	99.8 (99.1 to 100)	91.7 (76.0 to 100)	86.6 (84.1 to 89.0
9.5	98.5%	0	748	0	0	638	110	0%	100 (99.5 to 100)	N/A	85.3 (82.8 to 87.8)
10	99.1%	0	748	0	0	638	110	0%	100 (99.5 to 100)	N/A	85.3 (82.8 to 87.8)

Table 6 – Time to First Major Intervention

Major Intervention	Time from ED Arrival (Hours)	> 3 Hours to First Major Intervention	> 6 Hours to First Major Intervention	> 12 Hours to First Major Intervention
Surgery Only (n = 46)	1.5 [0.6 – 3.0]	10 (21.7%)	4 (8.7%)	3 (6.5%)
Embolization Only (n = 18)	5.3 (4.0 – 6.5]	15 (83.3%)	5 (27.8%)	1 (5.6%)
Massive Transfusion Only (n = 5)	3.5 [2.0 – 9.3]	3 (60.0%)	2 (40.0%)	0 (0%)
Two or More Major Interventions (n = 41)	1.5 [0.5 – 3.5]	12 (29.3%)	5 (12.2%)	2 (4.9%)
All Interventions (n = 110)	2.0 [1.0 – 4.0]	40 (36.4%)	16 (14.5%)	6 (5.4%)

Time to first major intervention is presented as median [Q1 – Q3]; Categorical variables are presented as n (%)

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Chapter 6 - Discussion

This chapter provides a summary of the thesis findings, highlights strengths and limitations, and outlines the next steps for future research including knowledge translation and dissemination.

6.1 Summary

In this thesis, the overall objective was to improve the risk stratification of bleeding trauma patients and therefore reduce the time to intervention and incidence of preventable death. In order to achieve this, we derived and internally validated a clinical prediction model for identifying which patients presenting to hospital with traumatic bleeding would ultimately require massive transfusion, embolization or surgery for hemostasis. To begin with, we reviewed the concept of traumatic hemorrhage assessment in Chapter 2, discussing the consequences of severe blood loss, the importance of early identification and limitations in the current literature that serves to guide this decision making. Cognizant of the common methodological missteps in clinical prediction modeling, we proceeded with a plan to pre-specify a model based on the best available literature and clinical expertise. In Chapter 3, we discussed the findings of a systematic review of clinical prediction models for traumatic hemorrhage intervention, commenting on the quality of the existing literature and identifying potential candidate predictors presented by sufficient quality studies. In Chapter 4, we reviewed the results of a national survey of Canadian traumatologists and their valuations of various predictors for traumatic hemorrhage intervention. In Chapter 5, we utilize these prior study findings in order to pre-specify predictive variables, and later refine and internally validate a clinical prediction model that identifies patients who will require an intervention to address their severe bleeding.

6.2 Key Study Findings

In this thesis, we conducted three studies that ultimately contributed to the derivation and internal validation of a clinical prediction model for the identification of bleeding trauma patients that will require a composite outcome of massive transfusion, embolization, or surgery for hemostasis. The first study, a systematic review and meta-analysis, identified the following important findings: (1) there are currently no clinical prediction models evaluating the composite outcome of interest, (2) many of the existing models were designed to identify only those requiring massive transfusion, (3) the existing literature generally failed to adhere to appropriate methodological standards and (4) seven candidate predictors (mechanism of injury, systolic BP, heart rate, hemoglobin, lactate and FAST ultrasound) were identified from sufficient quality models. The second study, a national survey of Canadian traumatologists, identified six candidate predictors (hemodynamics, clinical examination, FAST ultrasound, mechanism of injury, blood gases and CT imaging). The third study involved the derivation and internal validation of a clinical prediction model for traumatic hemorrhage intervention and provided the following key results: (1) a multivariable model was created based on pre-specification of predictors available within the first hour of resuscitation as identified from previous study findings, (2) the model was simplified to a five variable score (systolic BP, clinical examination, lactate, FAST and CT imaging) termed the Canadian Bleeding (CAN-BLEED) score, (3) the CAN-BLEED score demonstrated excellent sensitivity and specificity for identifying need for intervention in bleeding patients and (4) the reported times to intervention suggest the potential for improvement upon successful validation and implementation of the score.

6.3 Importance of Findings

This thesis work lays the foundational groundwork for an evidence-based, methodologically rigorous prediction model for risk stratifying bleeding trauma patients. The ultimate implementation of this model would provide clinicians with a practical, easy-to-use decision tool that assists with the quick and accurate assessment of hemorrhagic injuries. Appropriate risk stratification would theoretically allow for more rapid provision of necessary major interventions, as well as improve bleeding associated morbidity and mortality.

6.4 Strengths and Limitations

The primary strength of this thesis is the strict adherence to the highest methodological standards outlined by the PROGRESS group for clinical prediction modeling. By utilizing an approach based on pre-specification and avoidance of stepwise selection, we minimize the potential for overfitting or for type II error wherein important variables are erroneously removed as a result of sample size limitations. In addition, the comprehensive process of pre-specification incorporates the highest standard of integrative, evidence-based medicine wherein clinical expertise is used in conjunction with existing literature. Lastly, the strong influence of clinical expertise throughout the model derivation and refinement process offers significant optimism for functionality and successful implementation in the future.

The findings of this thesis should be interpreted with consideration of the following limitations. Despite our best efforts to minimize the effects of a modest sample size, the model is nonetheless refined and assessed in the setting of a small population from a single center with specialized resources and specific pathways for activation of certain interventions. As a result, external validation utilizing a different time, population and setting may certainly demonstrate a decline in model performance. In addition, the model does rely upon the incorporation of CT

imaging which requires both time and specialized resources not universally available in non-trauma centres. Lastly, the process of model specification did require subjective decision making and clinical expertise by an adjudication committee of local trauma surgeons and as such, model composition may have differed in another setting.

6.5 Conclusion & Next Steps

This thesis adopts the highest methodological standard for clinical prediction modeling, utilizing clinical expertise and existing literature in order to pre-specify a model for the early identification of the need for major intervention in bleeding trauma patients. A simple, five variable score, termed the Canadian Bleeding (CAN-BLEED) score is proposed, highlighting diagnostic findings available to the clinician within the first hour of assessment: systolic BP, clinical exam, lactate, FAST ultrasound and CT imaging. The model presents excellent sensitivity and specificity and potential for use as a valuable triage tool for clinicians.

While these preliminary findings are promising, there remains a need for assessment within a larger, external population. The engagement of the trauma community presented valuable opportunities for knowledge translation. A national, multi-disciplinary working group has been established with plans to conduct a multi-centre derivation and refinement study for the CAN-BLEED score. In addition, an international survey of Canadian, American, European and Australian trauma providers is planned in order to assess current challenges in traumatic hemorrhage assessment, barriers to timely delivery of intervention and desired functionality for a clinical prediction score. There is clearly a prime opportunity for innovation in the care of this high risk and vulnerable population. Our research team strives to refine, validate and ultimately implement a practical prediction score that allows clinicians to quickly and efficiently identify bleeding patients requiring an escalation of care in order to

activate the appropriate care pathway. Appropriate risk stratification would theoretically allow for more rapid provision of necessary major interventions, as well as improve bleeding associated morbidity and mortality. This methodologically rigorous multi-study research program offers considerable potential for identifying and alleviating inefficiencies in current decision-making and pathway-activating practices for hemorrhaging trauma patients. Ultimately, once validated and refined, we intend to advocate for the tool's widespread adoption and consideration of integration into the Advanced Trauma Life Support protocol for educating future trauma providers.

Appendix 1 – National Survey of Canadian Traumatologists

This appendix comprises the survey from the manuscript "Predictors to Identify Clinically Significant Bleeding in Trauma Patients: A National Survey of Canadian Traumatologists". It was distributed electronically via the Trauma Association of Canada to all 153 staff physician members in April 2017.

1. In what country do you currently practice as a traumatologist?

   Answer: _____

2. How many years have you been practicing as a traumatologist?

   Answer:

   - Less than 5 years
   - 5 to 10 years
   - 10 to 20 years
   - More than 20 years

3. What medical and ATLS training have you completed? (Please check all that apply)

   Answer:

   - Surgical residency
   - Emergency Medicine residency
   - Anesthesiology residency
   - Trauma fellowship
   - Critical Care fellowship
   - No ATLS certification
   - ATLS Provider certification
   - ATLS Instructor certification
   - Other (Please specify) _____

4. Which of the following best describes the trauma designation level of your current institution?

   Answer:

   - Level 1 (Comprehensive regional resource and tertiary care facility)

- Level 2 (Initiate definitive care with availability of general surgery, orthopedics, neurosurgery, anesthesiology, critical care)
- Level 3 (Prompt assessment, resuscitation and surgery with availability of general surgery and anesthesiology)
- Level 4 (24 hour laboratory coverage, provider ATLS assessment and stabilization prior to transfer of patients to high level trauma centre)
- Level 5 (Provide ATLS assessment and stabilization prior to transfer of patients to high level trauma centre)

5. How many trauma patients present to your institution each month with clinically significant bleeding requiring intervention for hemorrhage (hemostatic surgery, embolization, massive transfusion)?

Answer:

- Less than 1 patient per month
- 1 to 10 patients per month
- 11 to 30 patients per month
- More than 30 patients per month

6. The following question applies to your initial trauma assessment during the first hour in hospital. From the following list, please identify and rank your TOP FIVE most important variables you consider when evaluating a trauma patient's risk for clinically significant bleeding in order to determine he need for intervention, defined as hemostatic surgery, embolization or massive transfusion (#1 being most important). Variables not within the top five can be left without a ranking.

Answer:

- Patient demographics (age and sex) _____
- Mechanism of injury (penetrating vs. blunt) _____
- Glasgow coma scale _____
- Clinical evidence of hemorrhage (pelvic instability, bleeding wound) _____
- Hemodynamic vitals (systolic blood pressure, heart rate) _____
- Complete blood count (hemoglobin) _____
- Blood gases (pH, base deficit, lactate) _____
- Coagulation testing (INR) _____
- Focussed Abdominal Sonography for Trauma _____
- Computed Tomography Imaging (free fluid or active extravasation) _____

7. Which of the following descriptions of patient hemodynamics would be most useful for inclusion in a clinical prediction model for traumatic hemorrhage assessment?

Answer:

- Systolic BP < 90 (yes or no)
- Systolic BP < 110 (yes or no)
- Heart Rate > 120 (yes or no)
- Herat Rate > 100 (yes or no)
- Shock Index (Heart Rate / Systolic BP) > 1.0 (yes or no)

8. Which of the following descriptions of coagulopathy would be most useful for inclusion in a clinical prediction model for traumatic hemorrhage assessment?

Answer:

- INR > 1 (yes or no)
- INR > 1.5 (yes or no)
- INR > 2 (yes or no)

9. Which of the following descriptions of acid-base disturbance would be most useful for inclusion in a clinical prediction model for traumatic hemorrhage assessment?

Answer:

- Base deficit > 6 (yes or no)
- Base deficit > 10 (yes or no)
- Lactate > 5 (yes or no)
- Lactate > 10 (yes or no)
- pH < 7.25 (yes or no)

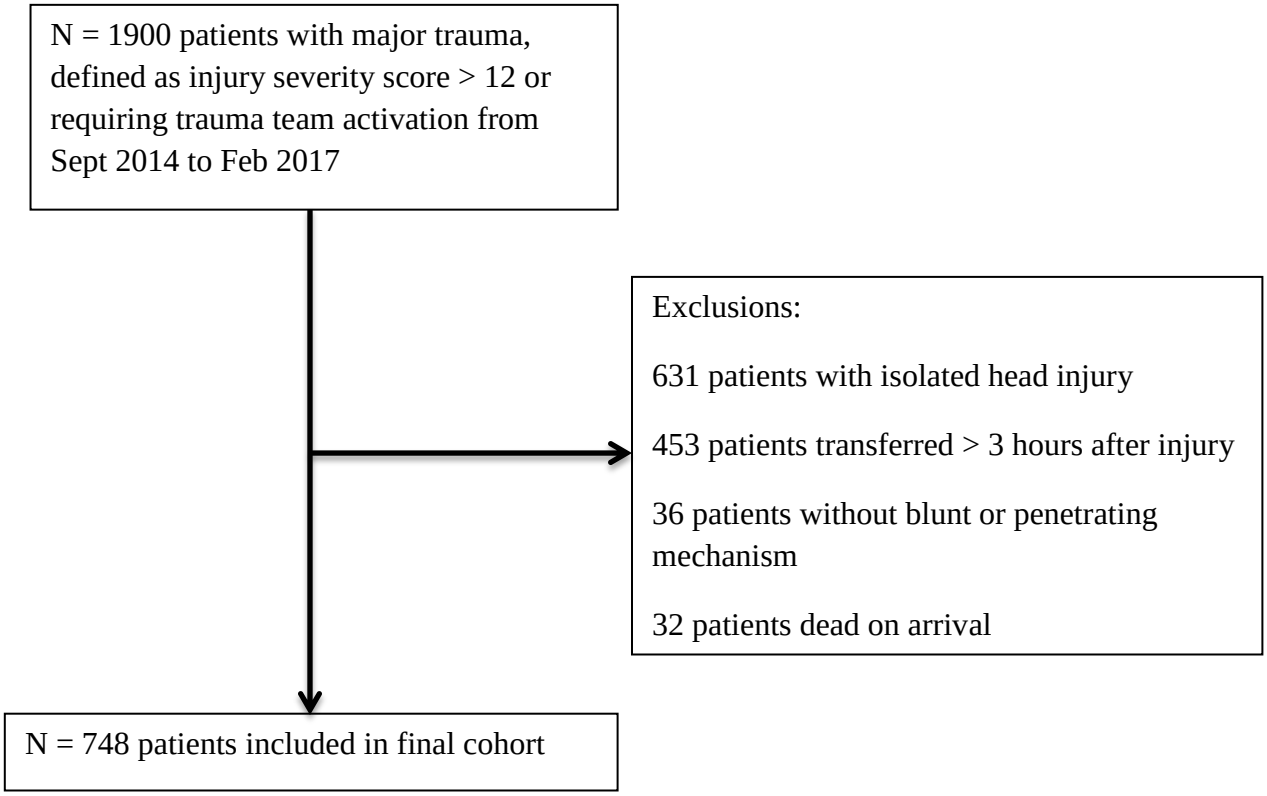
10. Which of the following descriptions of anemia would be most useful for inclusion in a clinical prediction model for traumatic hemorrhage assessment?

Answer:

- Hemoglobin < 70 (yes or no)
- Hemoglobin < 90 (yes or no)
- Hemoglobin < 110 (yes or no)

Appendix 2 – Patient Selection for Study Cohort

This appendix comprises the flow diagram describing patient selection for the manuscript "Early Identification of the Need for Major Intervention in Patients with Traumatic Hemorrhage: Development and Internal Validation of the Canadian Bleeding (CAN-BLEED) Score." Patients with major trauma were identified from the Ottawa Trauma Registry and charts were manually reviewed to determine eligibility.



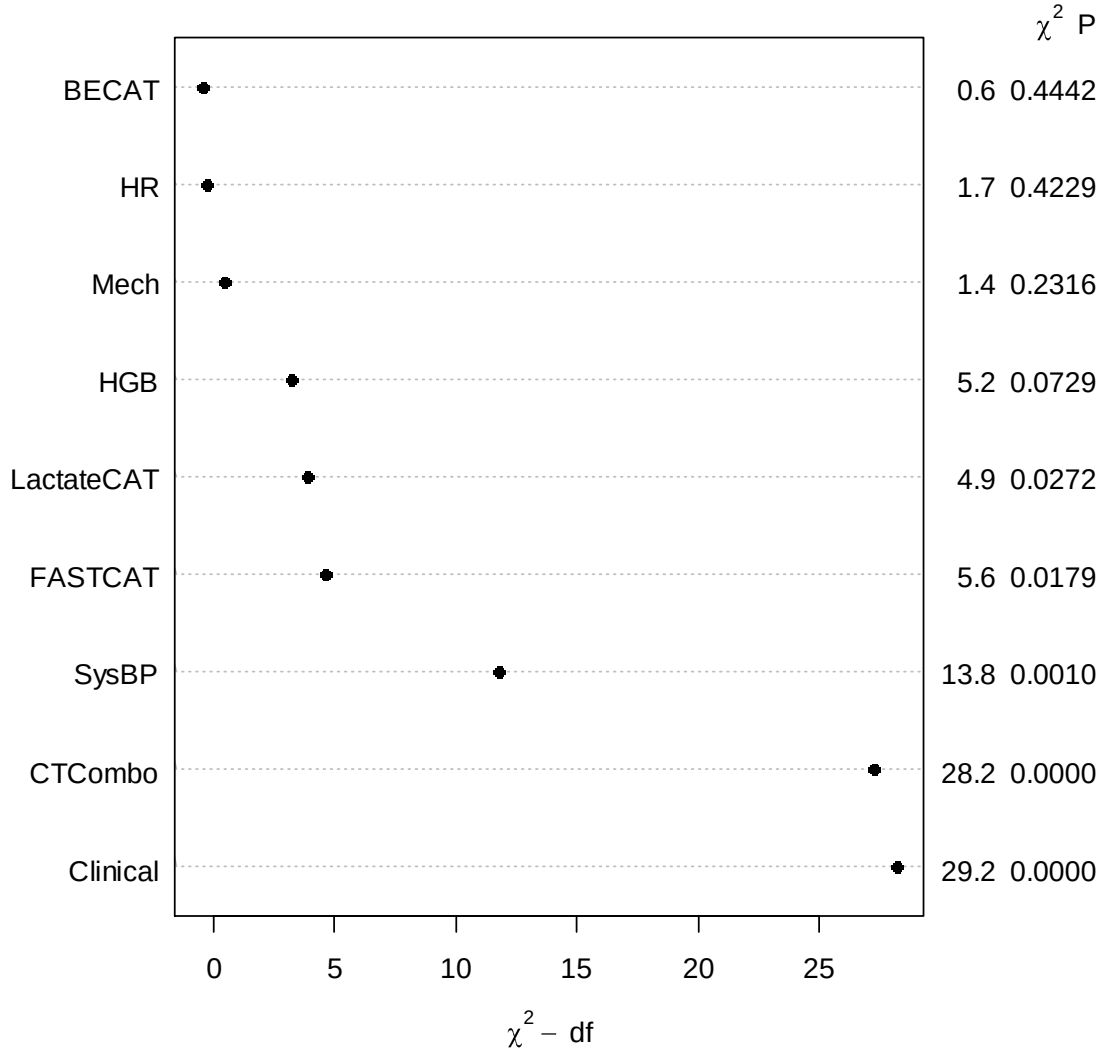
Appendix 3– Full Pre-Specified Model

This appendix comprises the full pre-specified model for the manuscript "Early Identification of the Need for Major Intervention in Patients with Traumatic Hemorrhage: Development and Internal Validation of the Canadian Bleeding (CAN-BLEED) Score." Findings from the systematic review and survey were reviewed by an adjudication committee of local trauma surgeons in order to select variables and allotted degrees of freedom for inclusion.

Variable	Coding Method	Valid Range/Levels	Degree of Freedom Allocation
Mechanism of Injury	Categorical	Penetrating, Blunt	1
Systolic BP	Continuous (RCS)	0 – 250 mmHg	2
Heart Rate	Continuous (RCS)	0 – 200 bpm	2
Clinical Exam suggestive of Hemorrhage	Categorical	Yes, No	1
FAST	Categorical	Positive, Negative	1
Hemoglobin	Continuous	0 – 250 g/L	1
Base Excess < -6	Categorical	Yes, No	1
Lactate > 5	Categorical	Yes, No	1
Free Fluid or Active Extravasation on CT	Categorical	Yes, No	1

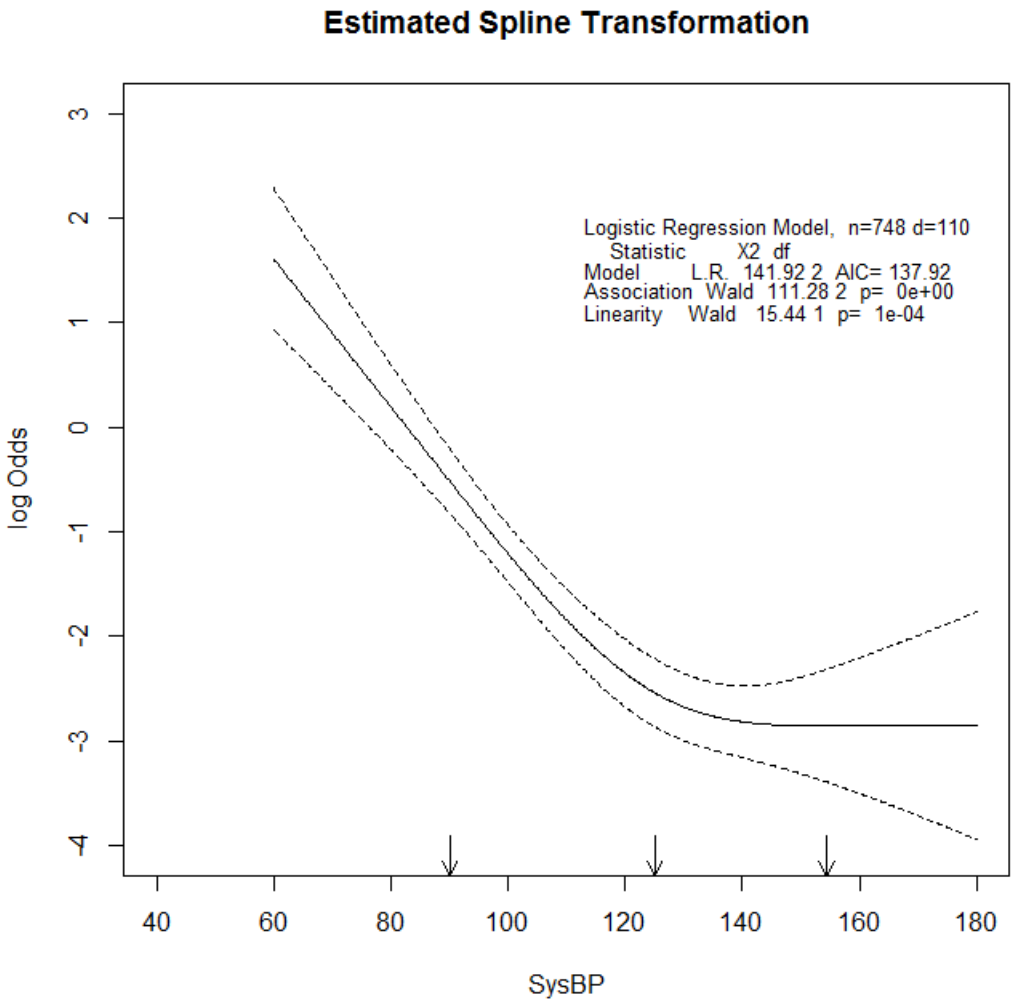
Appendix 4 – ANOVA Plot

This appendix comprises the ANOVA plot for the manuscript "Early Identification of the Need for Major Intervention in Patients with Traumatic Hemorrhage: Development and Internal Validation of the Canadian Bleeding (CAN-BLEED) Score." The relative importance of variables, accounting for Chi-Square test association with the composite outcome as well as allotted degrees of freedom, is described visually. The most important variables are presented in ascending order.



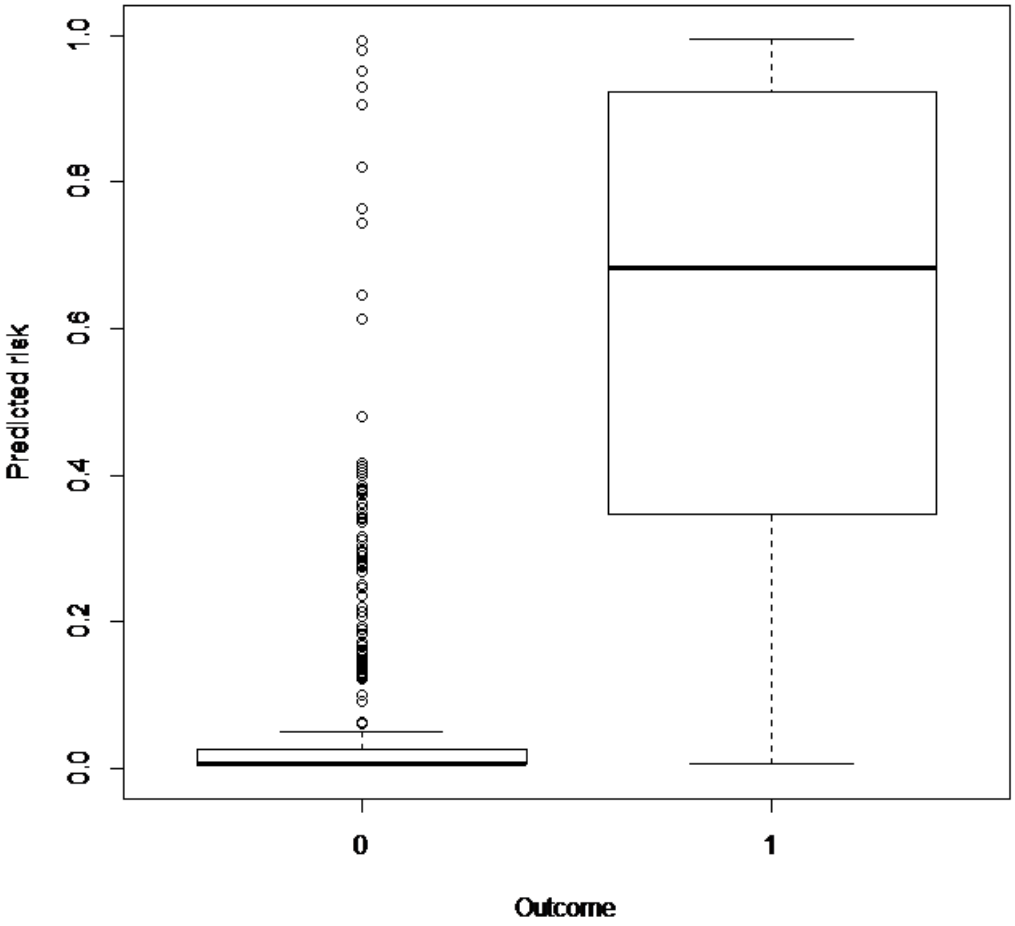
Appendix 5 – Cubic Spline Function for Systolic Blood Pressure

This appendix comprises the cubic spline function for systolic blood pressure for the manuscript "Early Identification of the Need for Major Intervention in Patients with Traumatic Hemorrhage: Development and Internal Validation of the Canadian Bleeding (CAN-BLEED) Score." In this plot, the function is modelled using three knots to describe the association between systolic blood pressure at varying levels and the log odds of the composite outcome.



Appendix 6 – Box Plot Assessment of Discrimination for Simplified Model

This appendix comprises the box plot assessment of discrimination for the manuscript "Early Identification of the Need for Major Intervention in Patients with Traumatic Hemorrhage: Development and Internal Validation of the Canadian Bleeding (CAN-BLEED) Score." The distribution of predicted risk is presented visually and demonstrates a clear difference between those with and without the composite outcome.



Appendix 7 – Calibration Plot Assessment for Simplified Model

This appendix comprises calibration assessment for the manuscript "Early Identification of the Need for Major Intervention in Patients with Traumatic Hemorrhage: Development and Internal Validation of the Canadian Bleeding (CAN-BLEED) Score." The close association between observed and predicted risk is presented visually.