

**THE IMPACT OF TIME TO MAJOR INTERVENTION AND DELAYED CARE FOR  
PATIENTS WITH TRAUMATIC HEMORRHAGE**

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## **Thesis Abstract**

Background: The specific clinical impact of delays to hemostatic intervention in trauma is under-explored.

Objectives: Investigate the current understanding of the impact of increasing time to hemostasis and assess its relationship with clinical outcomes.

Methods: We conducted a systematic review to characterize existing definitions of delayed hemostasis and its clinical sequelae. We conducted a cohort study of 147 trauma patients to investigate the impact of increased time to hemostasis.

Results: Most studies demonstrated significant relationships between time to hemostasis and mortality, despite heterogeneity. The cohort study failed to demonstrate a significant association between time to hemostasis and mortality.

Discussion: The thesis has taken steps to investigate time to hemostasis with appropriate methodology. The findings are limited by sample size and confounding by indication.

Conclusions: There remains a substantial gap in the literature with respect to understanding the impact of increasing time to hemostasis in trauma and larger studies are needed.

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## **Authors' Contributions**

Manuscript #1 – *The Impact of Time to Hemostatic Intervention and Delayed Care for Patients with Traumatic Hemorrhage: A Systematic Review*

Tyler Lamb (T.L.), Christian Vaillancourt (C.V.), Monica Taljaard (M.T.), and Jacinthe Lampron (J.L.) contributed to study conception and design. Abstract screening and full text review were performed in duplicate by T.L. and Alexandre Tran (A.T.). Data abstraction and risk of bias assessments were completed by T.L. Analysis was performed by T.L., while T.L., C.V., and M.T. contributed to data interpretation. The manuscript was drafted by T.L. All authors contributed to critical revisions and final approval.

Manuscript #2 – *The Impact of Time to Hemostatic Intervention and Delayed Care for Patients with Traumatic Hemorrhage: A Retrospective Cohort Study*

T.L., C.V., M.T., and J.L. contributed to study conception and design. Data extraction was completed by T.L. Statistical analysis was performed by T.L. with the guidance of M.T. and C.V. All authors contributed to the drafting of this manuscript, including critical revisions and final approval. Analysis was performed by T.L, M.T., and C.V. The manuscript was drafted by T.L. All authors contributed to critical revisions and final approval.

**Ethics Approvals**

Manuscript #1 – *The Impact of Time to Hemostatic Intervention and Delayed Care for Patients with Traumatic Hemorrhage: A Systematic Review*

Ethics approval was not required.

Manuscript #2 – *The Impact of Time to Hemostatic Intervention and Delayed Care for Patients with Traumatic Hemorrhage: A Retrospective Cohort Study*

Ethics approval was obtained from the Ottawa Health Science Network Research Ethics Board on September 29, 2021. Ethics renewal was obtained September 6, 2022.

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## **Chapter I – Introduction**

This chapter provides an overview of the objectives of the thesis, as well as a brief description of the included manuscripts.

### **1.1 Thesis Objectives**

The primary objective of the thesis was to investigate the current understanding of the impact of increasing time to hemostatic intervention among bleeding trauma patients, seeking to move beyond the dogma of the “golden hour” and the general stance that “faster is better”. Additionally, the thesis work intended to build on current literature by assessing the relationship between time to hemostasis and clinically relevant outcomes in a representative sample and with appropriate statistical methodological rigour.

More specifically, we sought to:

- i. Systematically review the literature to determine whether longer delay to surgery or angioembolization for hemostasis is associated with increased mortality, receipt of an increased volume of packed red blood cells, or a longer stay in hospital or the intensive care unit;
- ii. Provide a descriptive understanding of the temporal definition of delayed intervention based on a systematic review of the literature;
- iii. Conduct a retrospective cohort study to quantify the association between time to hemostatic intervention and in-hospital mortality and receipt of packed red blood cells in a local sample of bleeding trauma patients;

## **1.2 Overview of Thesis and Manuscripts**

### Chapter II – Background

This chapter reviews the importance of timely identification of traumatic hemorrhage, presents a number of barriers and delays to bleeding control, and describes the current evidence informing efforts to reduce delays to definitive trauma care. The relevant gaps in knowledge are explored and a rationale for the thesis work is presented.

### Chapter III – Systematic Review of the Literature

This chapter describes the weaknesses of the current body of literature related to time to hemostatic intervention and summarizes the contemporary understanding of the impact of delayed care. We present the published review manuscript, *The Impact of Time to Hemostatic Intervention and Delayed Care for Patients with Traumatic Hemorrhage: A Systematic Review* (Citation: Lamb T, Tran A, Lampron J, Shorr R, Taljaard M, Vaillancourt C. The Impact of Time to Hemostatic Intervention and Delayed Care for Patients with Traumatic Hemorrhage: A Systematic Review. J Trauma Acute Care Surg. 2023. DOI: 10.1097/TA.0000000000003976.).

### Chapter IV – Retrospective Cohort Study

The fourth chapter includes a preliminary, local observational study of the impact of increasing time to hemostasis among a representative sample of bleeding trauma patients. We present the second manuscript, *The Impact of Time to Hemostatic Intervention and Delayed Care for Patients with Traumatic Hemorrhage: A Retrospective Cohort Study*.

### Chapter V – Discussion

This chapter reviews the important findings of the thesis and describes the necessary steps to further advance the research program.

## **Chapter II – Background**

### **2.1 The Burden of Trauma**

Trauma is a significant cause of morbidity and mortality, with traumatic injuries representing the third leading cause of death in Canada in 2017.<sup>1</sup> Indeed, more than 18,000 Canadians died that year as a result of injuries and violence, with estimated nation-wide costs in excess of \$19.8 billion per year.<sup>1,2</sup> Nearly 16 million people, or 43% of the population, reside outside of a city with a level one trauma centre, and more than 22% of Canadians live greater than one hour from a dedicated trauma centre, which can affect timely access to care.<sup>3</sup> This care includes a multitude of investigations and therapies provided by physicians, surgeons, nurses, and many other health professionals, with definitive care often referring to surgical or interventional radiological techniques to stop bleeding and repair injuries.

### **2.2 Physiology and Identification of Traumatic Hemorrhage**

Uncontrolled bleeding remains the most common cause of preventable mortality in trauma.<sup>4</sup> Patients can decompensate rapidly, with 85% of hemorrhage-related deaths occurring within 24 hours.<sup>5</sup> In some patients, there is a clear presentation of physiologic extremis with acidosis, coagulopathy, hypothermia, and hypocalcemia.<sup>6-8</sup> However, in others, typical signs of hemorrhage may be less apparent.<sup>9</sup> Indeed, clinical gestalt has demonstrated a sensitivity of only 65.6% for prediction of need for massive transfusion, and the Advanced Trauma Life Support (ATLS) guidelines may overestimate the degree of tachycardia and hypotension associated with blood loss.<sup>9-11</sup> To date, a high-quality, evidence-based model to predict need for hemostatic intervention in traumatic hemorrhage has not been established, though there are ongoing efforts locally to do so.<sup>12,13</sup> The consequence of difficulties in identifying high-risk bleeding patients is delayed access to intervention, which may contribute to increased mortality.<sup>7,14,15</sup> Underscoring

the concerns around delayed intervention, an international survey of trauma care providers has identified delays in both the detection of clinically significant hemorrhage as well as the delivery of hemostatic interventions due to clinical and logistical barriers.<sup>16</sup> The nature of these barriers is heterogeneous, including difficulties in recognizing bleeding patients requiring intervention, issues with communication between team members, and perceived inefficiency of medical and non-medical staff.<sup>16</sup>

### **2.3 Knowledge Gap on Delays to Hemostatic Intervention**

The clinical problem is three-fold: [1] physiologic signs of significant hemorrhage remains elusive in its identification; [2] clinical gestalt and existing decision aids have performed poorly; and [3] systemic and cognitive issues lead to delays in the provision of hemostatic interventions. In Canada, much of the trauma system is designed to minimize delays and maximize efficiency at every opportunity. The core principle involves ensuring patients reach the appropriate location for the appropriate care as soon as possible. This includes development of what has been described as a “scoop and run” strategy for management of critical injuries by paramedics, thereby minimizing the time spent at a scene prior to transporting patients to hospital<sup>17-20</sup>; the bypass of community hospitals en route to designated, specialized trauma centres<sup>21,22</sup>; and coordinated responses at the trauma centres, wherein the appropriate subspecialists are urgently assembled and critical resources are placed on-hold in case they are needed (i.e. the computed tomography [CT] scanner is made available, an operating room is prepared and held, etc.).

While intuitive that delays in delivery of major hemostatic interventions – including surgery to obtain hemostasis and angioembolization of bleeding vessels – may be associated with adverse outcomes, the real-world clinical impacts of these delays are less clear. This may be due

in part to the nature of physiologic compensation for hemorrhage. That is, changes in vital signs may appear suddenly and drastically only when physiologic reserve is exhausted, leading to rapid decompensation and potentially mortality.<sup>23</sup> In this way, the effects of delayed hemostatic intervention to stem bleeding are likely to be non-linear and may be difficult to completely characterize.

Further, in addition to focusing on time to intervention for a broad range of bleeding and non-bleeding injuries, the existing literature has variably defined delayed intervention. Among studies investigating interventions for hollow viscus injuries in adults, a cut-off of 24 hours from presentation is perhaps the most frequently employed<sup>24–28</sup>, though other studies have used four hours<sup>14,29</sup>, eight hours<sup>30</sup>, or an hour-by-hour definition to assess delays<sup>31</sup>. In other instances, no time cut-offs are defined, and delay is based on patient transport between areas of the hospital (e.g. intensive care unit [ICU], diagnostic imaging, operating room, etc.).<sup>15</sup> Beyond differences in the temporal definition of delayed intervention, research to date has also differed in terms of the population of interest, the major intervention evaluated, and the nature of delay considered. For example, some aspect of delayed care has also been investigated in pediatric populations, as well as mixed populations of patients with head injuries, hemorrhagic injuries to the chest or abdomen, or hollow viscus injuries.<sup>14,15,24,32</sup> In some cases, only operative intervention was considered<sup>24,33</sup>, while others specifically investigated angioembolization.<sup>14</sup> A combination of multiple interventions is rarely considered.<sup>15</sup> With respect to defining delay, some researchers have focused on pre-hospital transport time and others have investigated the time from presentation to activation of the trauma team.<sup>17–20,34–36</sup> Physiologically, the true “time zero” is the time of injury, which is difficult to capture and therefore less frequently explored.

## **2.4 Summary and Thesis Rationale**

Bleeding represents a leading cause of mortality and is increasingly managed with a combination of surgical and interventional radiological techniques in addition to targeted, aggressive resuscitation with blood products. The current landscape of research investigating time to major intervention for traumatic hemorrhage includes the following: a general understanding that expedient intervention is preferred to delays, a heterogeneous body of literature with respect to subpopulations of trauma patients (ie. blunt vs penetrating) and interventions under consideration, and a diverse range of often arbitrary definitions of delayed intervention. That which remains unclear is the specific quantitative impact of delays to operative intervention and angioembolization on important patient outcomes such as mortality, length of stay, and functional status at discharge, as well as the broader systems-level impacts of these delays. It is clear that there are two primary needs: [1] consolidation of the extant literature in this area to provide better understanding of the current evidence and quantify the potential benefit of timely hemostatic intervention, and [2] further methodologically rigorous studies investigating the impacts of delayed major interventions for traumatic hemorrhage specifically.

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## **Chapter III – Systematic Review of the Literature**

### **3.1 Manuscript #1 – Systematic Review**

#### **The Impact of Time to Hemostatic Intervention and Delayed Care for Patients with Traumatic Hemorrhage: A Systematic Review**

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**PROSPERO Protocol Registration Number:** CRD42022319896. Further methodological details are provided in Appendix A.

**Protocol Amendments:** There were no protocol amendments.

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## Abstract

*Background:* Uncontrolled bleeding is a common cause of preventable mortality in trauma. While intuitive that delays to hemostasis may lead to worse outcomes, the impacts of these delays remain incompletely explored. This systematic review aimed to characterize the extant definitions of delayed hemostatic intervention and to quantify the impacts of delays on clinical outcomes.

*Methods:* We searched EMBASE, MEDLINE, and Web of Science from inception to August 2022. Studies defining “delayed intervention” and those comparing times to intervention among adults presenting to hospital with blunt or penetrating injuries who required major hemostatic intervention were eligible. The co-primary outcomes were mortality and the definition of delay to hemostasis employed. Secondary outcomes included units of packed red blood cells received, length of stay in hospital, and length of stay in intensive care.

*Results:* We identified 2,050 studies, with 24 studies including 10,168 patients meeting inclusion criteria. The majority of studies were retrospective observational cohort studies and most were at high risk of bias. A variety of injury patterns and hemostatic interventions were considered, with 69.6% of studies reporting a statistically significant impact of increased time to intervention on mortality. Definitions of delayed intervention ranged from ten minutes to four hours. Conflicting data were reported for impact of time on receipt of blood products, while one study found a significant impact on intensive care length of stay. No studies assessed length of stay in hospital.

*Conclusions:* The extant literature is heterogeneous with respect to injuries included, methods of hemostasis employed, and durations of delay examined. While the majority of the included studies demonstrated a statistically significant relationship between time to intervention and mortality, an evidence-informed definition of delayed intervention for bleeding trauma patients

at large has not been solidified. Additional, standardized research is needed to establish targets which could reduce morbidity and mortality.

## Background

Uncontrolled bleeding remains the most common cause of preventable mortality in trauma.<sup>1</sup> Patients can decompensate rapidly, with 85% of hemorrhage-related deaths occurring within 24 hours.<sup>2</sup> Some patients present with clear physiologic extremis, including acidosis, coagulopathy, and hypothermia.<sup>3-5</sup> However, in others, typical signs of hemorrhage may be less apparent.<sup>6</sup> Indeed, clinical gestalt has demonstrated a sensitivity of only 65.6% in predicting the need for massive transfusion, and the Advanced Trauma Life Support (ATLS) guidelines appear to overestimate the degree of tachycardia and hypotension associated with blood loss, decreasing the guidelines' ability to recognize severe blood loss when present.<sup>6-8</sup>

The consequence of difficulties in identifying high-risk bleeding patients is delayed intervention, which may contribute to increased mortality.<sup>4,9,10</sup> Underscoring the concerns around delayed intervention, an international survey of trauma care providers has identified clinical and logistical barriers leading to delays in both the detection of clinically significant hemorrhage as well as the delivery of interventions.<sup>11</sup> The nature of these barriers is heterogeneous, including difficulties in recognizing bleeding requiring intervention, issues with communication among team members, and inefficiencies in care delivery, such as suboptimal mobilization of medical and nonmedical support staff and preparation of operating rooms and angiography suites.<sup>11</sup>

While intuitive that delays in delivery of major interventions – including surgery to obtain hemostasis and angioembolization of bleeding vessels – may be associated with adverse outcomes, the real-world clinical impacts of these delays are less clear. Changes in vital signs may appear suddenly only when physiologic reserve is exhausted, leading to rapid decompensation and potentially mortality.<sup>12</sup> In this way, the effects of delayed intervention to stem bleeding are likely to be non-linear and may be difficult to completely characterize. Further,

in addition to focusing on time to intervention for a broad range of bleeding and non-bleeding injuries, the extant literature has variably defined “delayed intervention”.

It is clear that there is a need for consolidation of the published literature in this area to improve understanding of the current evidence and to quantify the potential benefits of timely hemostatic intervention. The aims of this systematic review were to characterize the contemporary understanding of the nature of delayed hemostasis and to quantify the impacts of such delays on relevant clinical outcomes. The primary objective was to determine whether longer delay to surgery or angioembolization for hemostasis is associated with increased mortality, as well as to provide a descriptive understanding of the temporal definition of delayed intervention. Secondary objectives included evaluating the impact of increasing time to hemostasis on blood products received and length of stay in hospital and in the intensive care unit (ICU).

## Methods

We used The Cochrane Handbook for Systematic Reviews of Interventions and The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) checklist to develop and report this systematic review.<sup>13,14</sup> The protocol was registered with PROSPERO (CRD42022319896). Ethics approval was obtained from the institutional research ethics board.

### *Eligibility Criteria*

The population of interest included adult patients presenting to hospital with blunt or penetrating injuries to the neck, thorax, abdomen, pelvis, or extremities and who required major hemostatic intervention for bleeding, including surgery or angioembolization, or a combination thereof. Patients with traumatic brain injuries were eligible for inclusion if they were included by individual study authors. Studies seeking to define “delayed intervention” for hemostasis, as well

as those comparing patients undergoing “delayed” interventions to those without delay or comparing time to intervention were eligible regardless of the definition of delay employed. Randomized controlled trials and observational cohort studies were eligible for inclusion. Case reports, case series with <5 patients, and case-control studies were excluded. Conference abstracts and grey literature were eligible for inclusion if they reported data on any outcome of interest. We included studies in either English or French with no date restrictions applied.

### *Information Sources and Search Strategy*

The search strategy was developed in collaboration with a qualified library information specialist and is presented in Appendix A. We searched EMBASE, MEDLINE, and the Web of Science from inception to January 2022. The search strategy was repeated on August 22, 2022. Reference lists of included studies were also reviewed to identify eligible studies not captured by our search. Titles, abstracts, and potentially eligible full texts were reviewed independently by trained reviewers (T.L. and A.T.). Data collection was performed independently by a single author (T.L.) using a standardized, piloted data collection tool. All discrepancies were resolved by consensus or a senior author (C.V.).

### *Outcomes*

The co-primary outcomes were overall mortality and the definition of delay to hemostasis employed in the studies. Secondary outcomes included units of packed red blood cells (pRBCs) received, length of stay in hospital, and length of stay in ICU.

### *Risk of Bias in Individual Studies*

Risk of bias for included studies was assessed by T.L. using the Risk of Bias in Non-Randomized Studies of Exposures (ROBINS-E) tool.<sup>15</sup> Evaluation of whether control of confounding was appropriate was based on inclusion of factors expected to be clinically relevant

for the examined patient population, as well as on whether an appropriate method of a priori confounder selection was described. Sample size was not a specific factor taken into account, nor was event-to-variable ratio.

### *Analysis*

Relevant characteristics of the included studies were incorporated into a narrative synthesis, grouped by the outcomes of interest. Summary measures for dichotomous outcomes including odds ratios or risk ratios with associated 95% confidence intervals, as well as hazard ratios with associated 95% confidence intervals for time-to-event data, were extracted from individual studies or calculated from the available data. The heterogeneity of patient populations, interventions, reported outcomes, and follow-up timeframes of included studies were reviewed by all authors to determine whether a meta-analysis was both feasible and appropriate.

## Results

### *Study Selection*

The literature search identified 1,928 unique records through database searching and an additional 27 records through searching studies' reference lists, for a total of 1,955 records. Title and abstract screening excluded 1,889 records and 66 full texts were evaluated. Twenty-four studies including 10,168 patients met full eligibility criteria.<sup>9,16-38</sup> Reasons for exclusion included different patient population (n=19), wrong exposure (n=18), wrong study design (n=4), and abstract without necessary data (n=1). The search strategy was repeated on August 22, 2022, revealing an additional 95 titles and abstracts to be screened. An additional two full texts were reviewed; one was in fact a duplicate and a second was an abstract without necessary data (Figure 1).

### *Study Characteristics*

Table 1 summarizes the characteristics of the included studies.<sup>9,16,25–34,17,35–38,18–24</sup> The two largest studies contributed 56.2% of the included patients (5,716/10,168)<sup>18,25</sup>, and 15/24 studies contained over 100 patients. One study was a prospective observational cohort<sup>36</sup>, one included analysis of prospectively collected randomized controlled trial data<sup>28</sup>, and the remainder were retrospective observational cohort studies. Fifteen studies took place in a single-centre and nine were multi-centre studies. All studies included trauma patients requiring surgery or angioembolization for hemostasis, though the specific injuries or means to obtain hemostasis varied between studies. Studies evaluating patients requiring only operative intervention for abdominal trauma were most common (n=9), followed by those evaluating patients requiring thoracic and/or neck surgery (n=4), angioembolization for pelvic fractures (n=4), surgery or angioembolization for any bleeding injuries (n=4), surgery for abdominal or chest injuries (n=2), and angioembolization for blunt abdominal solid organ injury (n=1). Twelve studies included patients with severe head injuries<sup>9,17,31,32,18,19,23,24,26–28,30</sup>, while 7 specifically excluded either all head injuries or those with head Abbreviated Injury Scale scores over 2. The remainder of studies did not comment on inclusion of patients with traumatic brain injuries.

### *Risk of Bias*

Risk of bias was assessed for all studies reporting on mortality, pRBCs received, hospital length of stay, or ICU length of stay (Figure 2). Nine studies (40.9%) were at very high risk of bias due to lack of control of confounding<sup>16,19,22,32,33,35–38</sup>, and, for Rosengart et al. (1999), very high risk of bias due to missing data.<sup>33</sup> An additional nine studies (40.9%) were at high risk of bias, as important confounders were not controlled for despite control of other confounders<sup>17,20,21,23,26,28–30,34</sup>. Two studies had some concerns with respect to bias, as potentially

relevant confounders such as heart rate were not controlled for, but their ultimate impact on the outcomes of interest was unclear.<sup>9,24</sup> Two studies were found to have low risk of bias.<sup>25,31</sup>

### *Study Outcomes*

Data for co-primary and secondary outcomes are presented in Tables 2 through 4. Due to substantial heterogeneity in included patient populations, as well as differences in individual study eligibility criteria, methodology, and definitions of “time to intervention”, meta-analysis was not methodologically appropriate. Instead, we present a narrative review below.

### *Primary Outcomes*

#### **Mortality**

Twenty-three of 24 studies had mortality or survival as outcomes of interest.<sup>9,16,25,26,28–35,17,36–38,18–24</sup> Most studies (15/23; 65.2%) reported in-hospital mortality, while four reported 30-day mortality, three examined 24-hour mortality, two assessed 28-day mortality, and one reported time to mortality (Table 1). Included studies also differed with respect to methods of analysis and time to intervention examined (Table 2). Multivariable logistic regression was the most frequently employed analysis method, with nine studies (39.1%) reporting the adjusted impact of time to intervention from one minute up to four hours. Three studies (13.0%) used proportional hazards regression, six (26.1%) reported unadjusted differences in time to intervention between survivors and decedents, three (13.0%) provided raw data or unadjusted odds ratios between specific time intervals, and one study (4.3%) reported each of a mixed-effects Poisson regression analysis and descriptive times to death.

In total, 16 studies (69.6%) reported a statistically significant impact of increased time to intervention on mortality. The majority of these studies examined time from emergency department (ED) arrival to either surgery or angioembolization, while one reported scene time,

three examined time from injury to ED arrival, and two performed analysis based on time from injury to surgery. In general, studies excluded patients transferred from another hospital. Statistically significant impacts of time intervals as great as six hours and as short as one minute were reported, with most studies examining delays of less than 60 minutes. Only one study specifically investigated delays of 60 minutes, or the “golden hour”. Among studies describing a significant impact of time to intervention on mortality, nine specifically included patients with only abdominal or pelvic injuries, four included any injuries requiring surgery or angioembolization, two included penetrating cardiac injuries, and one included thoracocervical injuries.

Among the six studies which did not find a significant impact of time to intervention on mortality, three focused on major abdominal vascular injuries, two included pelvic fractures undergoing angioembolization, and one included only resuscitative thoracotomies. All of these studies assessed delays to intervention of 90 minutes or less. Three of the six studies without statistical significance used unadjusted analyses, while the majority of studies employing adjusted analyses reported statistically significant results.

#### Definition of Delay

Six studies reported a definition for delayed hemostatic intervention, with each pertaining to a different subpopulation of trauma patients and none attempting to establish a definition for bleeding trauma patients at large, as was theorized with the “golden period”, contemporarily described as the “golden hour” (Table 3).<sup>39</sup> The least restrictive definition was posited by Stewart et al. (1994), who advocated for all trauma laparotomies to be performed within four hours of ED arrival, though the selected time cut-off was noted to be arbitrary.<sup>27</sup> Conversely, Meizoso and colleagues (2016) described the “golden 10 minutes” between the ED and operating room for

patients with thoracoabdominal gunshot wounds and hypotension, as delays beyond this were significantly associated with mortality and 50% of patients who died had done so by 16 minutes.<sup>20</sup> Similarly, targets for on-scene time and transport time of less than 10 minutes each were described by Mina et al. (2017) for patients with penetrating cardiac injuries based on univariate analysis.<sup>21</sup>

Other proposed definitions of delay included 90 minutes from ED arrival to surgery for injuries to the aorta and IVC<sup>16</sup>, and three to four hours from injury to hospital arrival for liver injuries requiring surgery.<sup>36</sup> Time cut-offs appeared to be selected after initial review of the data rather than a priori, where this information was provided. Remick and colleagues (2014) analyzed time to mortality for patients who died from penetrating injuries within four hours, from which they concluded that delays of 43 minutes from injury to surgery would result in 50% mortality, while reducing this time to 19 minutes would potentially salvage 95% of patients.<sup>18</sup> Interestingly, no study specifically reaffirmed the target of the “golden hour”.

### Secondary Outcomes

Secondary study outcomes for transfusion requirements and length of stay are presented in Table 4.

#### Transfusion Requirements

Two studies reported on requirements for pRBC transfusion.<sup>9,36</sup> Butt et al. (2006) reported mean numbers of “blood bags” – presumably corresponding to units of pRBCs – by time from injury to ED arrival, noting increases in blood product transfusions with increased time.<sup>36</sup> For example, patients presenting within two hours required a mean of 1-3 bags, compared to greater than 12 bags for those presenting between eight and 10 hours.<sup>36</sup> The authors did not perform any additional statistical analysis to quantify the impact of time on transfusion needs.

Chehab and colleagues (2020) analyzed differences in 24-hour pRBC transfusion volumes between patients reaching angioembolization from the ED for blunt abdominal solid organ injury at increasing one hour intervals up to four hours.<sup>9</sup> Analysis employing the Mann-Whitney *U* test did not reveal statistically significant differences between patients in each of the four temporally-defined groups.<sup>9</sup>

#### Length of Stay

Hospital length of stay was not reported as a factor of time to hemostasis or delayed intervention in any included study. Chou et al. created a multivariable linear regression model for patients undergoing angioembolization for pelvic fracture, noting that time from ED “to angioembolization was an independent indicator of ICU length of stay ( $p=0.015$ )”.<sup>26</sup>

#### Discussion

This systematic review identified 24 studies including 10,168 patients and evaluated the impact of increased time to hemostatic intervention on mortality, pRBCs received, length of stay in hospital and ICU, as well as proposed definitions of delayed intervention in the literature. Trauma patients undergoing a variety of surgical and interventional radiological procedures were included, with 69.6% of included studies noting a significant impact of time to intervention on mortality. This increased to 76.9% of studies when considering only those that attempted to adjust for relevant confounders. Definitions of delayed intervention ranged from ten minutes to four hours across a variety of injury-specific subpopulations.

The notion that reduced time to hemostasis should improve clinical outcomes is intuitive. This is most clearly captured by the prevailing dogma of trauma’s “golden hour”, wherein definitive care should be delivered within 60 minutes of injury.<sup>39</sup> However, it is important to acknowledge that this was first posited nearly 40 years ago with relatively little supporting

evidence, and there have been substantial changes to trauma care and systems since. As such, it is not unreasonable to suggest that in current systems, the “golden hour” may over- or underestimate the critical time to intervention, depending on the specific patient, injury pattern, or setting. It is for this reason that objective, appropriately adjusted data are needed to quantify the true impact of time to hemostasis on outcomes. However, this systematic review demonstrates that the extant literature is heterogeneous with respect to injuries included, methods of hemostasis employed, and, importantly, durations of delay examined. There is also substantial variation in the inclusion of patients with head injuries. Even when included, the proportion of patients with severe brain injuries ranged from 0.7% to 71.1%, with as many as 58.0% of mortalities in one study coming as a result of head injuries as opposed to bleeding.<sup>18,28,31</sup> Earlier bleeding control for other injuries is not expected to improve such mortality, and consequently, inclusion of these patients is a potentially substantial confounder that must be addressed. Further, it is also clear that additional studies exploring the relationship of time to hemostasis and other clinical outcomes, such as length of stay and blood products received, are required, as these outcomes are potentially associated with significant costs and morbidity not captured in studies of mortality alone.

Our search strategy did not identify any reviews of objective definitions of delayed intervention for traumatic hemorrhage. Individual studies have primarily pertained to abdominal trauma and range from periods of ten minutes up to four hours after hospital arrival. The proposed definitions were generally developed based on individual study data, but this systematic review demonstrates that there exists marked heterogeneity in what period of increased time to hemostatic intervention may be statistically significant. It therefore remains unclear what constitutes a clinically significant delay to hemostasis for bleeding trauma patients

as a whole or in terms of specific injury patterns. Indeed, not all injuries are created equal, and the critical time to intervention is likely to vary between mechanisms of injury, as studies described herein have demonstrated. Important to note also is the time period being measured, as many studies reported time from hospital arrival to intervention, likely due to feasibility and reliability. Prehospital times may vary widely based on geography, population density, and trauma systems, and the impact of this period should be considered in the assessment of delays to care. Of similar importance is the role of interfacility transfer, which is an integral part of the trauma system not explored by most included studies. At our Level I trauma centre, over 40% of trauma patients are transferred from peripheral hospitals. The outcomes of these patients are equally important but comparatively under-researched, suggesting a need for a more pragmatic approach to investigating time to hemostasis in trauma.

Additionally, further studies are needed to examine robust, multi-centre data with adequate control of confounding, assessment of possible interactions and effect modification between variables, and to reconcile expert opinions in order to work towards a consensus definition of delayed intervention in trauma. Further, there needs to be a rigorous commitment to appropriate statistical analysis, as many studies to date have inadequately controlled for relevant confounders or have used unadjusted analyses. This would expand on the imprecise, intuitive position that “faster is better”, as has been seen in other areas of medicine and surgery, such as the establishment of target “door-to-balloon” times in cardiology.<sup>40</sup> This would have important health systems and policy implications, potentially leading to improved urban planning to facilitate transfer of as many trauma patients as possible within a prespecified interval, as well as informing trauma bypass protocols to ensure patients are being routed to centres capable of achieving definitive hemostasis.

In terms of mortality outcomes, over two thirds of included studies reported a significant impact of increased time to intervention. This is consistent with the common understanding that delays may lead to worse clinical outcomes, but the current body of literature does not clarify what period of time prior to hemostasis may serve as an objective target to reduce mortality. This is not an indictment of the current literature, but more of an acknowledgement of the difficulties associated with evaluating the impact of time and delays on death from bleeding. Specifically, while this review demonstrates that studies with adjustment for confounding generally reported statistically significant impacts of time to intervention on mortality, there are likely numerous unmeasured confounders and inherent subjectivity in decision making for the complex, heterogenous population that is trauma patients. Additionally, most studies to date have employed logistic regression analysis or unadjusted analyses, which may not fully account for the fact that time to intervention may vary as a factor of patient stability and clinical status in ways that may not be fully captured by adjustment for confounders. That is, time to intervention is likely to be shortest in the sickest patients, and adjustment for confounding may not completely mitigate this bias. Further studies utilizing proportional hazards regression may help to address this. Specifically, there may need to be accounting for time-dependent bias, which is often present and needs to be adequately controlled for to reach reliable conclusions.<sup>41</sup>

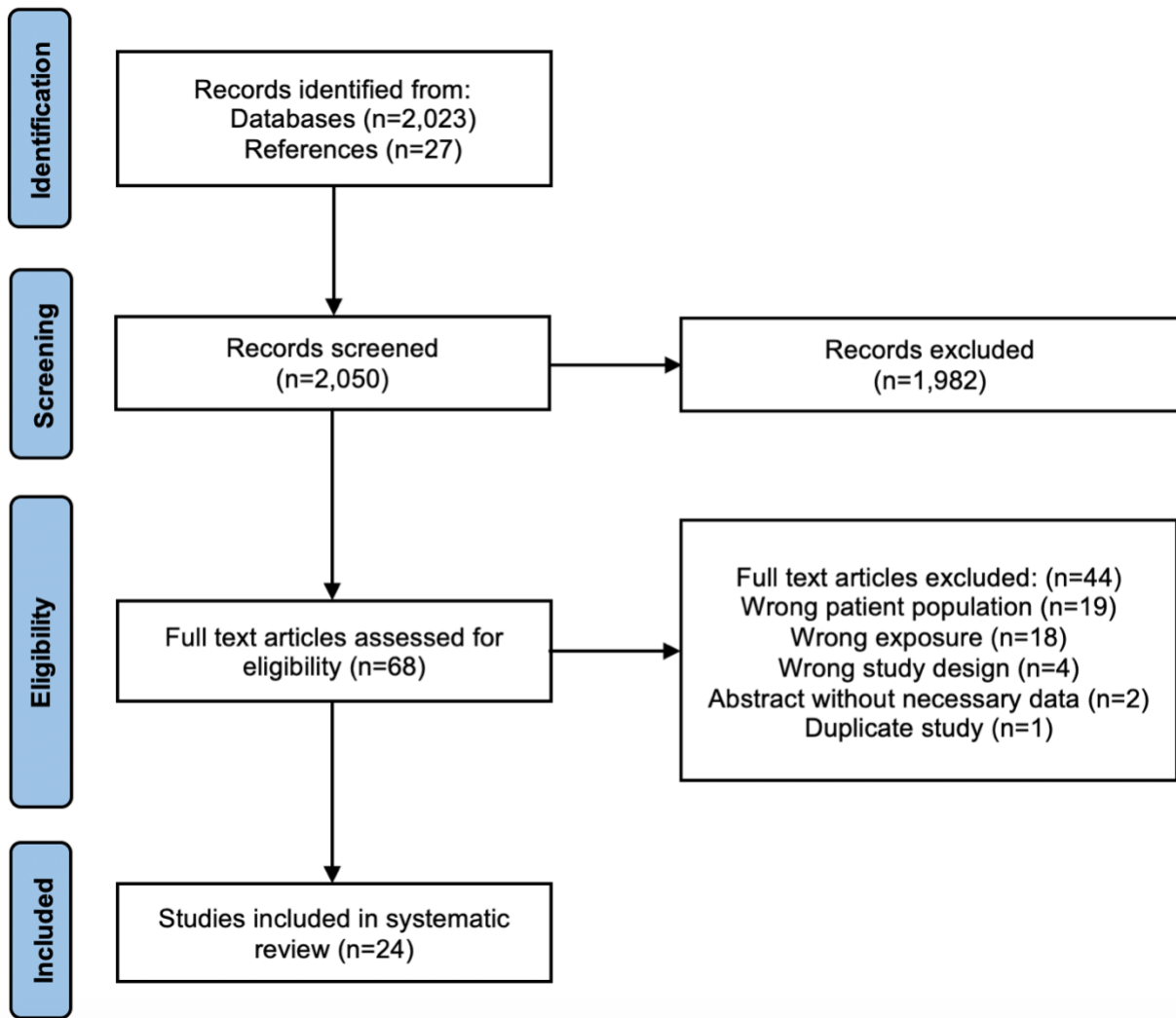
While this review has demonstrated that existing definitions of delayed hemostatic intervention in trauma vary in terms of patients and interventions considered, and that studies to date have presented a wide variety of conclusions with respect to delays of significance in a multitude of subpopulations, it certainly does have limitations. Given the heterogeneous patient populations, methods of analysis, and measures of time used, meta-analysis was not considered methodologically appropriate. With respect to the co-primary outcome of definition of delay to

hemostasis, we acknowledge that a systematic review is capable only of illustrating the definitions that currently exist in a descriptive fashion. Evaluation of these definitions and the eventual proposal of a broad, evidenced-informed definition will require large observational studies with appropriate adjustment for confounding, meta-analysis with reasonably homogenous data, or both. However, an understanding of the definitions previously proposed and their limitations is an essential first step toward further efforts to define delayed hemostasis in trauma.

Due to the nature of the included studies, this systematic review is unable to assess the relationship between time to hemostatic intervention and other relevant outcomes, such as missed injuries or potentially unnecessary interventions such as negative laparotomy. Additionally, one cannot include older studies without acknowledging the significant advancements in trauma care and resuscitation, particularly shifts to balanced blood product transfusion and more recent advancements such as whole blood use.<sup>42</sup> We also acknowledge that time is one of many interconnected factors that affect patient outcomes, and this review serves to further the discussion on optimizing efficiency in trauma care. Further, this systematic review includes a broad variety of trauma patients, injury patterns, and methods of hemostasis, and this breadth may be considered a limitation by some, as it precludes pooled analyses. However, as evidenced by the heterogeneity of contemporary research in this area, there is a demonstrable need for standardization of research efforts, and this review serves as a necessary precursor to more completely understanding and addressing the impact of avoidable and unavoidable delays in the care of bleeding trauma patients at large.

In conclusion, the prevailing dogma in trauma care has centred around the importance of the “golden hour”, but to date, an evidence-informed definition of delayed hemostatic intervention has not been solidified. Various studies have explored the relationship between

increased time to hemostasis in trauma and mortality, and the majority have described statistically significant relationships between time to intervention and mortality. However, these studies have examined diverse patient populations, injuries, and times of interest. There is a clear need for additional research with rigorous control of confounding as well as increased standardization of patient eligibility and times to intervention examined. While time is only one of many important factors that dictate outcomes, the goal remains the establishment of targets to which to aspire in order to reduce morbidity and mortality in the trauma patients for which we care.



**Figure 1.** PRISMA flow diagram.

| Study           | Risk of bias domains |    |    |    |    |    |    | Overall |
|-----------------|----------------------|----|----|----|----|----|----|---------|
|                 | D1                   | D2 | D3 | D4 | D5 | D6 | D7 |         |
| Halpern 1979    | ●                    | +  | +  | +  | +  | +  | +  | ●       |
| Flum 1997       | ●                    | +  | +  | +  | +  | +  | +  | ●       |
| Rosengart 1999  | ●                    | +  | +  | +  | ●  | +  | +  | ●       |
| Clarke 2002     | ⊗                    | +  | +  | +  | +  | +  | +  | ⊗       |
| Eachempati 2002 | ●                    | +  | +  | +  | +  | +  | +  | ●       |
| Butt 2006       | ●                    | +  | +  | +  | +  | +  | +  | ●       |
| Sikhondze 2007  | ●                    | +  | +  | +  | +  | +  | +  | ●       |
| Gui 2012        | ●                    | +  | +  | +  | +  | +  | +  | ●       |
| Barbosa 2013    | ⊗                    | +  | +  | +  | +  | +  | +  | ⊗       |
| Tanizaki 2014   | ●                    | +  | +  | +  | +  | +  | +  | ●       |
| Meizoso 2016    | ⊗                    | +  | +  | +  | +  | +  | +  | ⊗       |
| Miná 2017       | ⊗                    | +  | +  | +  | +  | +  | +  | ⊗       |
| Tezcan 2017     | ●                    | +  | +  | +  | +  | +  | +  | ●       |
| Tesoriero 2017  | ⊗                    | +  | +  | +  | +  | +  | +  | ⊗       |
| Matsushima 2018 | -                    | +  | +  | +  | +  | +  | +  | -       |
| Oliver 2019     | +                    | +  | +  | +  | +  | +  | +  | +       |
| Chou 2019       | ⊗                    | +  | +  | +  | +  | +  | +  | ⊗       |
| Chang 2019      | ⊗                    | +  | +  | +  | +  | +  | +  | ⊗       |
| Chehab 2020     | -                    | +  | +  | +  | +  | +  | +  | -       |
| Otsuka 2020     | ⊗                    | +  | +  | +  | +  | +  | +  | ⊗       |
| Hsieh 2021      | ⊗                    | +  | +  | +  | +  | +  | +  | ⊗       |
| Murao 2021      | +                    | +  | +  | +  | +  | +  | +  | +       |

Domains:  
D1: Bias due to confounding.  
D2: Bias arising from measurement of the exposure.  
D3: Bias in selection of participants into the study (or into the analysis).  
D4: Bias due to post-exposure interventions.  
D5: Bias due to missing data.  
D6: Bias arising from measurement of the outcome.  
D7: Bias in selection of the reported result.

Judgement  
● Very high  
● High  
- Some concerns  
+ Low

**Figure 2.** Risk of bias assessment using the Risk of Bias in Non-Randomized Studies of Exposures (ROBINS-E) tool.

**Table 1.** Characteristics of the 24 Included Studies.

| Author     | Year | Study Design                          | Region          | Population  | Patients | Outcomes                               |
|------------|------|---------------------------------------|-----------------|---|----------|--|
| Halpern    | 1979 | Single Centre<br>Retrospective Cohort | USA             | IVC and aortic injuries with<br>hypotension requiring laparotomy                                | 20       | Mortality, Delay<br>Definition         |
| Stewart    | 1994 | Multi-Centre<br>Retrospective Cohort  | USA             | Trauma laparotomies   | 110      | Delay Definition                       |
| Flum       | 1997 | Multi-Centre<br>Retrospective Cohort  | USA             | Thoracocervical vascular injuries<br>requiring surgery  | 16       | Mortality (30d)                        |
| Rosengart  | 1999 | Single Centre<br>Retrospective Cohort | USA             | IVC injuries requiring surgery  | 21       | Mortality                              |
| Clarke     | 2002 | Single Centre<br>Retrospective Cohort | USA             | Isolated bleeding abdominal injuries<br>requiring laparotomy                                    | 243      | Mortality                              |
| Eachempati | 2002 | Single Centre<br>Retrospective Cohort | USA             | Penetrating abdominal vascular injuries<br>requiring laparotomy                                 | 31       | Mortality                              |
| Butt       | 2006 | Single Centre<br>Prospective Cohort   | Pakistan        | Hepatic injuries requiring laparotomy   | 57       | Mortality, Delay<br>Definition, pRBCs  |
| Sikhondze  | 2007 | Single Centre<br>Retrospective Cohort | South<br>Africa | Hepatic injuries requiring laparotomy   | 105      | Mortality                              |
| Gul        | 2012 | Single Centre<br>Retrospective Cohort | Turkey          | Abdominal vascular injuries requiring<br>laparotomy   | 17       | Mortality                              |
| Barbosa    | 2013 | Multi-Centre<br>Retrospective Cohort  | USA             | Trauma laparotomies within 90<br>minutes, receiving $\geq 1$ u pRBCs, and<br>with positive FAST | 115      | Mortality (24h and<br>30d)             |
| Remick     | 2014 | Multi-Centre<br>Retrospective Cohort  | USA             | Penetrating trauma with death within 4<br>hours   | 2,533    | Time to Mortality,<br>Delay Definition |
| Tanizaki   | 2014 | Single Centre<br>Retrospective Cohort | Japan           | Hemodynamically unstable pelvic<br>fractures requiring AE                                       | 24       | Mortality                              |
| Meizoso    | 2016 | Single Centre<br>Retrospective Cohort | USA             | Torso GSWs with hypotension<br>requiring surgery  | 309      | Mortality, Delay<br>Definition         |
| Mina       | 2017 | Single Centre<br>Retrospective Cohort | USA             | Penetrating cardiac injuries  | 80       | Mortality, Delay<br>Definition         |
| Tezcan     | 2017 | Single Centre<br>Retrospective Cohort | Turkey          | Penetrating cardiac injuries  | 112      | Mortality                              |

|            |      |                                       |        |  |       |                                      |
|------------|------|---------------------------------------|--------|--|-------|--------------------------------------|
| Tesoriero  | 2017 | Single Centre<br>Retrospective Cohort | USA    | Pelvic fractures requiring AE within 12 hours  | 344   | Mortality                            |
| Matsushima | 2018 | Multi-Centre<br>Retrospective Cohort  | USA    | Pelvic fractures requiring AE within 4 hours   | 181   | Mortality, pRBCs (24h), LOS, ICU LOS |
| Oliver     | 2019 | Multi-Centre<br>Retrospective Cohort  | USA    | Trauma thoracotomies within 1 hour of ED arrival   | 3,183 | Survival                             |
| Chou       | 2019 | Single Centre<br>Retrospective Cohort | Taiwan | Pelvic fractures requiring AE directly from ED   | 84    | Mortality, ICU LOS                   |
| Chang      | 2019 | Multi-Centre<br>Prospective Cohort    | USA    | Trauma patients requiring surgery or AE for hemostasis within 1.5 hours                    | 408   | Mortality (30d)                      |
| Chehab     | 2020 | Multi-Centre<br>Retrospective Cohort  | USA    | Blunt abdominal solid organ injury requiring AE within 4 hours                             | 924   | Mortality (24h), pRBCs (24h)         |
| Otsuka     | 2020 | Single Centre<br>Retrospective Cohort | Japan  | Trauma patients with ISS $\geq 16$ and sBP < 90mmHg requiring surgery or AE for hemostasis | 125   | Survival                             |
| Hsieh      | 2021 | Multi-Centre<br>Retrospective Cohort  | Asia   | Trauma patients requiring surgery or AE for hemostasis within 1.5 hours                    | 963   | Mortality (30d)                      |
| Murao      | 2021 | Single Centre<br>Retrospective Cohort | Japan  | Blunt trauma with ISS $\geq 16$ , CT within 1.5 hours, and surgery or AE for hemostasis    | 163   | Mortality (28d)                      |

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*IVC* inferior vena cava, *pRBCs* packed red blood cells, *FAST* focused assessment with sonography in trauma, *AE* angioembolization, *GSW* gunshot wound, *ED* emergency department, *ISS* injury severity score, *sBP* systolic blood pressure, *CT* computed tomography, *LOS* length of stay, *ICU* intensive care unit.

**Table 2.** Impact of Time to Intervention on Mortality, by Analysis Type.

| Study   | Patients | Time Measure     | Mortality    | Effect Size  | p Value |
|---|----------|------------------|--------------|--|---------|
| <i>Multivariable Proportional Hazards Regression</i>  |          |                  |              | <i>Hazard Ratio (95% Confidence Interval)</i>                                  |         |
| Barbosa 2013  | 115      | ED to Surgery    | 20.0%        | HR <sub>(10min. increase)</sub> 1.58 (1.18-2.10)                               | p=0.002 |
| Meizoso 2016  | 309      | ED to Surgery    | 27.2%        | HR <sub>(11-60min. vs. ≤10 min.)</sub> 1.89 (1.10-3.26)                        | p=0.021 |
| Murao 2021  | 163      | ED to Surgery/AE | Not reported | “Earlier [surgery/AE] significantly associated with improved 28-day mortality” | p=0.026 |
| <i>Multivariable Logistic Regression</i>              |          |                  |              | <i>Odds Ratio (95% Confidence Interval)</i>                                    |         |
| Clarke 2002   | 243      | ED to Surgery    | 40.3%        | OR <sub>(1min. increase)</sub> 1.01 (NR)                                       | p<0.05  |
| Mina 2017   | 80       | Scene Time       | 41.3%        | OR <sub>(&lt;10min. vs. ≥10min.)</sub> 0.003 (0.00-0.11)                       | p<0.01  |
| Tesoriero 2017  | 344      | ED to AE         | 18.0%        | OR <sub>(1min. increase)</sub> 1.00 (0.996-1.002)                              | p=NS    |
| Matsushima 2018                                       | 181      | ED to AE         | 21.0%        | OR <sub>(60min. increase)</sub> 1.79 (1.11-2.91)                               | p=0.018 |
| Oliver 2019   | 3,183    | Injury to ED     | 80.2%        | OR <sub>(Survival; 11-20min. vs. ≤10min.)</sub> 0.57 (0.16-2.30)               | p=0.40  |
|   |          |                  |              | OR <sub>(Survival; 21-30min. vs. ≤10min.)</sub> 0.48 (0.14-1.92)               | p=0.27  |
|   |          |                  |              | OR <sub>(Survival; 31-40min. vs. ≤10min.)</sub> 0.53 (0.15-2.16)               | p=0.35  |
|   |          |                  |              | OR <sub>(Survival; 41-50min. vs. ≤10min.)</sub> 0.80 (0.22-3.35)               | p=0.75  |
|   |          |                  |              | OR <sub>(Survival; 51-60min. vs. ≤10min.)</sub> 0.77 (0.20-3.29)               | p=0.71  |
| Chou 2019   | 84       | ED to AE         | 16.7%        | OR <sub>(1min. increase)</sub> 1.015 (0.996-1.034)                             | p=0.126 |
| Chehab 2020   | 924      | ED to AE         | 15.4%        | OR <sub>(1-2hr. vs. ≤1hr.)</sub> 1.41 (1.22-2.42)                              | p=0.013 |
|   |          |                  |              | OR <sub>(2-3hr. vs. ≤1hr.)</sub> 1.69 (1.48-3.13)                              | p=0.021 |
|   |          |                  |              | OR <sub>(3-4hr. vs. ≤1hr.)</sub> 3.72 (1.51-5.11)                              | p=0.018 |
| Otsuka 2020   | 125      | ED to Surgery/AE | 50.0%        | OR <sub>(Survival; 1min. increase)</sub> 0.97 (0.96-0.99)                      | p<0.001 |
| Hsieh 2021  | 963      | Injury to ED     | 9.4%         | OR <sub>(30min. increase)</sub> 2.24 (0.45-11.23)                              | p=NS    |
|   |          | ED to Surgery/AE |              | OR <sub>(30min. increase)</sub> 7.10 (1.91-26.39)                              | p<0.05  |
| <i>Multivariable Mixed-Effects Poisson Regression</i> |          |                  |              | <i>Risk Ratio (95% Confidence Interval)</i>                                    |         |
| Chang 2019  | 408      | ED to Surgery/AE | 9.6%         | RR <sub>(15min. decrease)</sub> 0.97 (0.94-0.99)                               | p<0.001 |

| <i>Time for Survivors and Deceased (Minutes)</i> |     |                   |         | <i>Mean (SD)/Median [IQR]; Statistical Test</i>     |         |
|--|-----|-------------------|---------|---|---------|
| Flum 1997  | 16  | Injury to ED      | 25.0%   | 33.4 (13.3) vs. 50.8 (6.5); t-test                  | p<0.05  |
|  |     | ED to Surgery     |         | 46.5 (8.7) vs. 48.0 (16.3); t-test                  | p=NS    |
| Rosengart 1999                                   | 21  | Injury to ED      | 51.4% † | 47.4 [NR] vs. 33.0 [NR]                             | p=NS    |
|  |     | ED to Surgery     |         | 45.6 [NR] vs. 42.6 [NR]                             | p=NS    |
|  |     | Scene Time        |         | 21.1 (5.4) vs. 9.1 (1.8); ANOVA                     | p=0.105 |
| Eachempati 2002                                  | 31  | Transport Time    | 35.5%   | 12.9 (4.9) vs. 19.0 (14.8); ANOVA                   | p=0.651 |
|  |     | ED to Surgery     |         | 32.9 (6.9) vs. 50.3 (20.4); ANOVA                   | p=0.341 |
| Gul 2012   | 17  | Injury to Surgery | 23.5%   | 97.3 (16.1) vs. 140.0 (18.2); Mann-Whitney <i>U</i> | p=0.003 |
| Tanizaki 2014                                    | 24  | ED to AE          | 50.0%   | 63.1 (23.5) vs. 89.9 (28.6); t-test                 | p<0.05  |
| Tezcan 2017                                      | 112 | Injury to ED      | 12.5%   | 30.8 (15.4) vs. 53.2 (17.8); t-test                 | p=0.001 |

| <i>Unadjusted Odds Ratios (from Raw Data)</i> |     |                   |       | <i>Odds Ratio (95% Confidence Interval)</i>              |        |
|---|-----|-------------------|-------|--|--------|
| Halpern 1979                                  | 20  | ED to Surgery     | 65.0% | OR <sub>(≥1.5hr. vs. &lt;1.5hr.)</sub> 2.67 (0.24-30.07) | p=0.43 |
| Butt 2006                                     | 57  | Injury to ED      | 17.5% | OR <sub>(≥4hr. vs. &lt;4hr.)</sub> 14.50 (1.69-124.24)   | p=0.01 |
| Sikhondze 2007                                | 105 | Injury to Surgery | 19.0% | OR <sub>(≥6hr. vs. &lt;6hr.)</sub> 0.24 (0.08-0.79)      | p=0.02 |

*Time to Death (Descriptive)*

|             |       |               |      |                          |     |
|-------------|-------|---------------|------|--------------------------|-----|
| Remick 2014 | 2,533 | Time to Death | 100% | TD5: 19min.; TD50 43min. | N/A |
|-------------|-------|---------------|------|--------------------------|-----|

*ED* emergency department, *HR* hazard ratio, *AE* angioembolization, *OR* odds ratio, *NR* not reported, *NS* not significant, *RR* risk ratio, *SD* standard deviation, *IQR* interquartile range, *ANOVA* univariate analysis of variance, *TD5* time to death for 5<sup>th</sup> percentile, *TD50* time to death for 50<sup>th</sup> percentile, *N/A* not applicable.

† Time data were available for 21 patients, but overall mortality was reported for a cohort of 37 patient

**Table 3.** Definitions of Delay as Reported by Included Studies.

| <b>Study</b> | <b>Patient Population</b>                                     | <b>Definition of Delay</b>  | <b>Development of Definition</b>  |
|--------------|---|---|---|
| Halpern 1979 | IVC and aortic injuries with hypotension requiring laparotomy | 1.5 hours from ED arrival to surgery  | Authors observed that patients were “essentially unsalvageable” beyond this |
| Stewart 1994 | Trauma laparotomies   | 4 hours from ED arrival to surgery  | Arbitrary   |
| Butt 2006    | Hepatic injuries requiring laparotomy                         | 3-4 hours from injury to ED   | Authors observed that mortality “increase[d] drastically” beyond this       |
| Remick 2014  | Penetrating trauma with death within 4 hours                  | 19 minutes from injury to surgery to prevent 95% of mortalities;<br>43 minutes from injury to surgery to prevent 50% of mortalities | Distribution of times to death  |
| Meizoso 2016 | Torso GSWs with hypotension requiring surgery                 | 10 minutes from ED to surgery   | Proportional hazards regression   |

*IVC* inferior vena cava, *ED* emergency department, *GSW* gunshot wound.

**Table 4.** Impact of Time to Intervention on pRBC Transfusion and ICU Length of Stay.

| <b>Study</b>              | <b>Patients</b> | <b>Time Measure</b> | <b>Outcome Reporting</b>   | <b>p Value</b> |
|---------------------------|-----------------|---------------------|--|----------------|
| <i>pRBC Transfusion</i>   |                 |                     |  |                |
| Butt 2006                 | 57              | Injury to ED        | Increasing mean transfusion volume with additional 1-hour increases  | NR             |
| Chehab 2020               | 924             | ED to AE            | No significant difference in pRBC volume at 24 hours with increasing time to AE (Mann-Whitney <i>U</i> test) | p=0.154        |
| <i>ICU Length of Stay</i> |                 |                     |  |                |
| Chou 2019                 | 84              | ED to AE            | “Time to AE was an independent indicator of ICU length of stay” (Multivariable linear regression)            | p=0.015        |

*pRBC* packed red blood cells, *ICU* intensive care unit, *ED* emergency department, *NR* not reported, *AE* angioembolization

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## **Chapter IV – Retrospective Cohort Study**

### **4.1 Manuscript #2 – Retrospective Cohort Study**

#### **The Impact of Time to Hemostatic Intervention and Delayed Care for Patients with Traumatic Hemorrhage**

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## Abstract

*Background:* Uncontrolled bleeding is the most common cause of preventable death in trauma. The clinical effects of increased time to operative or radiological hemostatic intervention remain unclear. The overall aim of the study was to determine the impact of increased time to hemostatic intervention on mortality and transfusion requirements.

*Methods:* This retrospective observational cohort study included patients aged 16 or older presenting to a Canadian level I trauma centre between January 2016 and June 2021 and requiring hemostatic intervention within five hours of arrival. The primary outcome was in-hospital mortality and the secondary outcome was total volume of packed red blood cells transfused in hospital. We created a multivariable Cox proportional hazards regression model to estimate the association between time to hemostatic intervention and mortality. A multivariable linear regression model was used to assess the impact of time to intervention on volume of packed red blood cells transfused.

*Results:* One hundred forty-seven patients met inclusion criteria, with a median time to hemostatic intervention of 102.0 minutes [IQR 69.0-165.0]. Most patients were severely injured (median ISS 22.0 [IQR 13.0-33.0]). A total of 25 patients (17.0%) died in hospital and the time to intervention associated with 50% cumulative mortality was 78 minutes. Increasing time to intervention was not statistically significantly associated with increased mortality (aHR<sub>(1 min. increase)</sub> 0.99, 95% CI 0.99-1.00). Patients with intervention after 60 minutes received approximately 582mL fewer pRBCs compared to the early group, though this was not statistically significant (p=0.37).

*Conclusions:* This preliminary study failed to demonstrate a statistically significant association between increased time to hemostatic intervention and reduced mortality or decreased receipt of

blood products. These findings are likely the result of sample size limitations and confounding by indication. There remains a need for objective characterization of the impact of time to hemostatic intervention on mortality and blood transfusion requirements with larger, multicentre studies.

## Background

Uncontrolled bleeding is the most common cause of preventable death in trauma patients, with 85% of hemorrhage related deaths occurring within 24 hours.<sup>1,2</sup> For decades, the dogma within trauma care has hinged on the importance of the “golden hour”.<sup>3</sup> However, this was initially proposed nearly 40 years ago with relatively little supporting evidence. There have been significant advancements in trauma resuscitation and care since then, including the establishment of regional trauma systems, improved automotive safety standards, and more sophisticated prehospital care. The prevailing understanding therefore centres on the nonspecific notion that “faster is better”.

However, there are frequent delays to hemorrhage control (or hemostasis), and these delays occur for a variety of reasons. There may be logistical barriers to care delivery, including availability of trained personnel or accessibility of operating or interventional radiological suites, as well as clinical and cognitive factors.<sup>4</sup> Specifically, there may be difficulties in detecting clinically important bleeding, as the classically-described triad of acidosis, coagulopathy, and hypothermia may not always be present and Advanced Trauma Life Support (ATLS) guidelines may underestimate the amount of blood loss associated with normal heart rate and blood pressure.<sup>5–10</sup> The existing literature primarily includes studies examining a variety of injuries, methods of hemostasis, and durations of delay. These delays may be associated with adverse outcomes, but a more complete characterization of these adverse outcomes is lacking.<sup>9,11,12</sup> Consequently, the specific impact of delayed hemostatic intervention on mortality and other important clinical outcomes remains unclear. Indeed, a recent systematic review confirms that an evidence-informed definition of delayed intervention for bleeding trauma patients at large, along with the true impacts of such delays, have not been established.<sup>13</sup> In examining the body of

literature in this area, it becomes clear there is a need for pragmatic studies investigating the impact of delays to hemostasis in a representative, contemporary cohort of bleeding trauma patients, employing rigorous statistical analysis with adequate control of confounding.

### *Aims and Objectives*

The overall aim of the study was to conduct a preliminary investigation of the impact of increased time to operative or interventional radiologic hemostatic intervention on clinically important outcomes. The primary objective was to quantify the association between time to hemostatic intervention and in-hospital mortality. The secondary objective involved describing the association between time to hemostatic intervention and receipt of packed red blood cells (pRBCs).

### Methods

#### *Study Design and Setting*

This retrospective observational cohort study included patients presenting to The Ottawa Hospital Civic Campus, the regional level I trauma centre, between January 2016 and June 2021. The Ottawa Hospital cares for over 900 trauma patients each year, with a catchment area of 1.3 million people in two provinces and one territory. Trauma teams are staffed by general surgery residents in-house 24 hours per day with trauma team leaders (trauma surgeons or emergency physicians) required to be present within 20 minutes of activation. Trauma team activation is dependent upon a set of standardized criteria and reserves the emergency department CT scanner and a dedicated operating room for the trauma patient to minimize delays.

#### *Patient Population*

Eligible patients included those with traumatic injuries 16 years of age or older presenting from the scene and requiring major hemostatic intervention for injuries to the neck,

thorax, abdomen, pelvis, or extremities within five hours of arrival, or dying from bleeding prior to receipt of intervention. The five-hour threshold was selected in order to minimize heterogeneity among included patients. That is, those patients able to tolerate such a lengthy interval to hemostasis are likely to be inherently different than those requiring rapid hemostasis, introducing bias. Of note, there is precedent for use of a five-hour threshold, which has previously been employed in the study of time to intervention for hollow-viscus injuries.<sup>14</sup> Major hemostatic intervention was defined as surgery for hemostasis or angioembolization, or a combination thereof, with the indication being identification and cessation of bleeding. We excluded burns, electrocutions, drownings, and non-hemorrhagic mechanisms of injury, as well as patients who presented without a pulse or measurable blood pressure, even if they underwent resuscitative thoracotomy. Additionally, patients were excluded if they had an eligible injury but also had a catastrophic brain injury that was not believed to be survivable by the neurosurgery team as documented in the medical record. Ethics approval was obtained from the Ottawa Health Science Network Research Ethics Board.

### *Data Collection*

Patients were identified from The Ottawa Hospital Trauma Registry, a locally maintained and prospectively collected database. All cases included in the database were classified as a major trauma, defined as cases with an Injury Severity Score (ISS) greater than 12, trauma team activation, or requirement of hospitalization. Data were collected from review of the electronic medical record (Epic Systems Corporation, Madison, Wisconsin, USA) as well as The Ottawa Hospital Data Warehouse. A standardized data collection form was created and piloted prior to use. Data collection was performed by T.L., and any uncertainties were reviewed with senior authors (J.L., C.V.) to reach consensus.

### *Outcomes*

The primary outcome was in-hospital mortality, while the secondary outcome of interest was total volume of pRBCs, measured in mL, transfused during hospital admission. The main exposure of interest was time to hemostatic intervention (measured in minutes) from emergency department arrival to the start of the operative or interventional radiological procedure as documented prospectively in the medical record.

### *Statistical Analysis*

We calculated descriptive statistics for baseline patient demographics and clinical data, using medians and interquartile ranges if skewed (or means and (standard deviations) if normally distributed) for continuous variables, and frequencies and percentages for categorical variables. We compared demographics, hemodynamic parameters, injury severity, and mortality between patients with early hemostatic intervention (within 60 minutes of hospital arrival – the “golden hour”) versus late intervention (beyond 60 minutes) using Fisher’s exact or Mann Whitney U tests.

Time to hemostatic intervention for patients who survived and those who died was presented descriptively using box plots. To estimate the unadjusted association between time to hemostatic intervention and mortality, we first fitted a Cox proportional hazards regression analysis with the only independent variable specified as time to intervention. Length of stay was measured in minutes from the time of the intervention until either discharge (censoring) or death, so as to avoid attributing the time spent waiting for the intervention (the exposure of interest) to the hazard of the outcome. Time to intervention was modelled as a continuous variable. To estimate the adjusted association between time to hemostatic intervention and mortality, we conducted a multivariable Cox proportional hazards regression model by including covariates

that were believed to be clinically relevant and likely to have a meaningful impact on mortality. These included mechanism of injury (blunt or penetrating), age (years), Injury Severity Score (ISS), heart rate (beats per minute) and systolic blood pressure (mmHg) on arrival (as continuous variables), and Glasgow Coma Scale (GCS) score on presentation. No relevant interaction terms were identified for incorporation into the model. The model was used to calculate an adjusted hazard ratio (aHR) and associated 95% confidence interval (95% CI) for the explanatory variable of interest – time to hemostatic intervention.

Secondary outcome analysis involved a multivariable linear regression model assessing the impact of time to intervention on volume of pRBCs transfused. The outcome variable, pRBCs, was skewed and was therefore log transformed. However, this did not improve the distribution, which was skewed due to clinically expected and relevant outliers, so untransformed values were used in the analysis. Covariates expected to be predictive of need for blood transfusion were included in the model: mechanism of injury (blunt or penetrating), age, ISS, and heart rate and systolic blood pressure on arrival, as defined previously. Assessment of residuals confirmed the linearity assumption was appropriate. The model was used to calculate an adjusted difference and associated 95% CI for the explanatory variable of interest: time to hemostatic intervention, dichotomized at a cut-point of 60 minutes, as well as modelled continuously. There were no missing data for any included covariates in the cohort. Statistical significance was set at  $p < 0.05$ . All statistical analyses were performed using SAS On Demand software (SAS Institute Inc., Cary, North Carolina, USA).

## Results

### *Patient Characteristics*

One hundred forty-seven patients met inclusion criteria and were included in the analysis (Figure 1). Their characteristics are presented in Table 1. Patients most commonly underwent operative intervention (83.7%), with a median time to hemostatic intervention of 102.0 minutes [IQR 69.0-165.0] for the cohort at large. Almost all patients (90.0%) received at least one unit of pRBCs. They were predominantly male (77.6%) with a median age of 36.0 years [IQR 27.0-56.0] and were severely injured overall (median ISS 22.0 [IQR 13.0-33.0]). There were similar proportions of blunt and penetrating injuries. Patients were generally tachycardic but normotensive on presentation, with a mean heart rate of 100 beats per minute (SD 28.9) and median systolic blood pressure of 120mmHg [IQR 103-146]. Patients were usually fully alert with a median GCS of 15 [IQR 11-15]. Median length of stay was 9.0 days [IQR 4.0-21.0] in hospital and 1.0 days [IQR 0.0-4.0] in ICU.

Patients in the early intervention group (<60 minutes, n=24) had more penetrating injuries and lower GCS, while heart rate and systolic blood pressure were similar (Table 1). There were trends towards an increased proportion of males in the early group, as well as lower ISS and a greater proportion of patients undergoing operative intervention, though these were not statistically significant differences on unadjusted analyses (Table 1).

### *Mortality*

Twenty-five patients (17.0%) died in hospital. The majority of patients who died did so early in their admission, with a median time to mortality of 24 hours [IQR 2.9-96.0]. Mortality in the early group (<60 min.) was 33.3% (8/24), compared to 13.8% (17/123) in the late group. Among those who died, median time to hemostatic intervention was 78.0 minutes, compared to 104.5 minutes for survivors (Figure 2). Time to intervention was plotted against mortality, which revealed that the interval associated with 50% cumulative mortality was 78 minutes.

On unadjusted analysis, increasing time to intervention was not associated with statistically significant higher mortality ( $HR_{(1 \text{ min. increase})} 1.00$ , 95% CI 0.99-1.00). After controlling for clinically relevant covariates, increasing time to intervention, measured in minutes, was not statistically significantly associated with increased mortality ( $aHR_{(1 \text{ min. increase})} 0.99$ , 95% CI 0.99-1.01).

### *pRBC Transfusion*

Patients received a median of 1,402 mL of pRBCs (IQR 600-2,874), or approximately 4.67 units.<sup>15</sup> There was no significant difference in receipt of pRBCs between the early and late groups on unadjusted analysis (1,524 mL vs. 1,393mL,  $p=0.44$ ). On multivariable linear regression analysis, patients in the later intervention group received approximately 582mL fewer pRBCs compared to the early group, though this was not statistically significant ( $p=0.37$ ; Table 3). When time to intervention was modelled as a continuous variable, each additional increase of one minute to intervention was associated with receipt of approximately 2.2mL less pRBCs, but this was not statistically significant ( $p=0.52$ ).

### Discussion

This local, preliminary retrospective observational cohort of 147 severely injured trauma patients with bleeding that required surgical or interventional radiological hemostasis failed to demonstrate a statistically significant association between increased time to hemostatic intervention and mortality. Greater time to intervention was associated with a reduction in transfused pRBCs, though this was not statistically significant.

A recent systematic review has underscored the heterogeneity of previous studies investigating time to hemostatic intervention in trauma patients.<sup>13</sup> Indeed, a wide variety of mechanisms of injury, patterns of injury, and methods of hemostasis have been explored, usually

in isolation. Intuitively, nearly 70% of studies included in that systematic review reported a statistically significant association between increased mortality and greater time to intervention, but only two previous studies have investigated time to surgical or interventional radiological hemostasis in trauma patients as a whole, with both demonstrating a statistically significant reduction in mortality with decreased time to intervention.<sup>13,16,17</sup> That systematic review also investigated receipt of pRBCs as a factor of time to hemostatic intervention, with one study showing an unanalyzed increase with larger time intervals, and another showing no statistically significant association.<sup>13,18,19</sup>

The notion that “faster is better” in trauma care is intuitive, though this was not demonstrated in this preliminary study. The dogma in trauma resuscitation and care has centred around the “golden hour”, or the notion that definitive care should be delivered within one hour of injury. This principle extends to resuscitation with blood products as well, with recent evidence demonstrating that a greater interval between emergency medical services arrival and initiation of blood product transfusion or tranexamic acid is associated with increased mortality.<sup>20</sup>

The assertion that this study is sufficient to discredit a large volume of research and intuitive clinical wisdom would be misguided, and the lack of statistically significant findings is likely a consequence of uncontrolled confounding and small sample size. Specifically, while our sample included patients over a five year period, the overall sample was considerably smaller than some similar studies, which included upwards of several hundred or even thousands of patients.<sup>13,21,22</sup> As a result, the risk of type II error was elevated and the included sample may not be adequately representative of the population of bleeding trauma patients in a North American context.

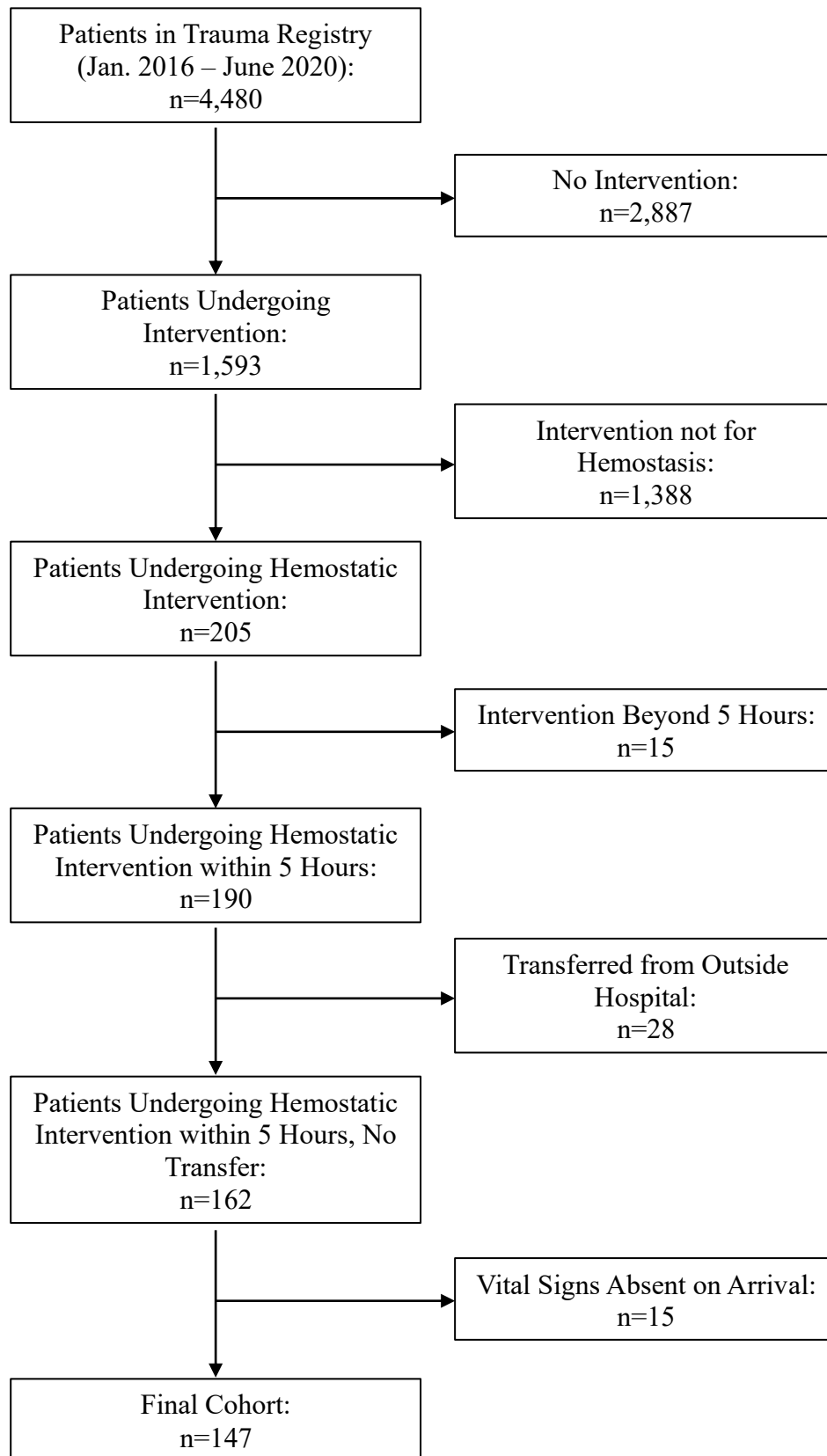
Our study has a number of important limitations. With respect to confounding, efforts were undertaken to control for factors that could be predictive of mortality or receipt of pRBCs, including mechanism of injury, age, ISS, heart rate, systolic blood pressure, and GCS, consistent with previous literature.<sup>13</sup> Despite this, the exposure groups of interest were likely inherently different – even when controlling for important predictors, patients undergoing hemostasis within 60 minutes are the most profoundly injured in a way not entirely captured by ISS and vital signs. The potential for confounding by indication is therefore considerable. Indeed, the early group contained almost exclusively penetrating injuries, which can be life-threatening despite a lower ISS, which may not be the best predictor of injury severity in this subpopulation despite its widespread use.<sup>23</sup> Secondly, the early group had a significantly lower initial GCS (13 vs. 15), which may be associated with increased mortality for reasons not related to hemorrhage. Thirdly, the imbalance between groups despite efforts to control for confounding was also likely exacerbated by the included time intervals for each group, which were carefully selected after thorough review of data for our centre. That is, the late group contained patients undergoing hemostatic intervention up to five hours after presentation, and from a clinical perspective it is not unreasonable to assume such patients may be inherently different than those requiring intervention – or dying – within one hour of arrival to hospital. Additionally, while this study focused exclusively on surgery and angioembolization, the medical aspects of hemorrhage control are of undeniable importance. This includes tranexamic acid administration, timely receipt of blood products (including more novel approaches such as whole blood transfusion), temporary mechanical hemostasis (ie. pressure or binders), and even more basic factors such as warming, which were not considered herein. Finally, the single-centre nature of the study does not allow for consideration of logistical differences between trauma centres, which may affect

generalizability. Specifically, interventional radiology is not in-house at our centre, so all patients requiring angioembolization are subject to some degree of delay, with only one angioembolization patient being included in the early group. The true impact of time to intervention may therefore be more accurately described with a larger, multi-centre study, where surgeons and interventional radiologists are more frequently in the hospital, minimizing delay.

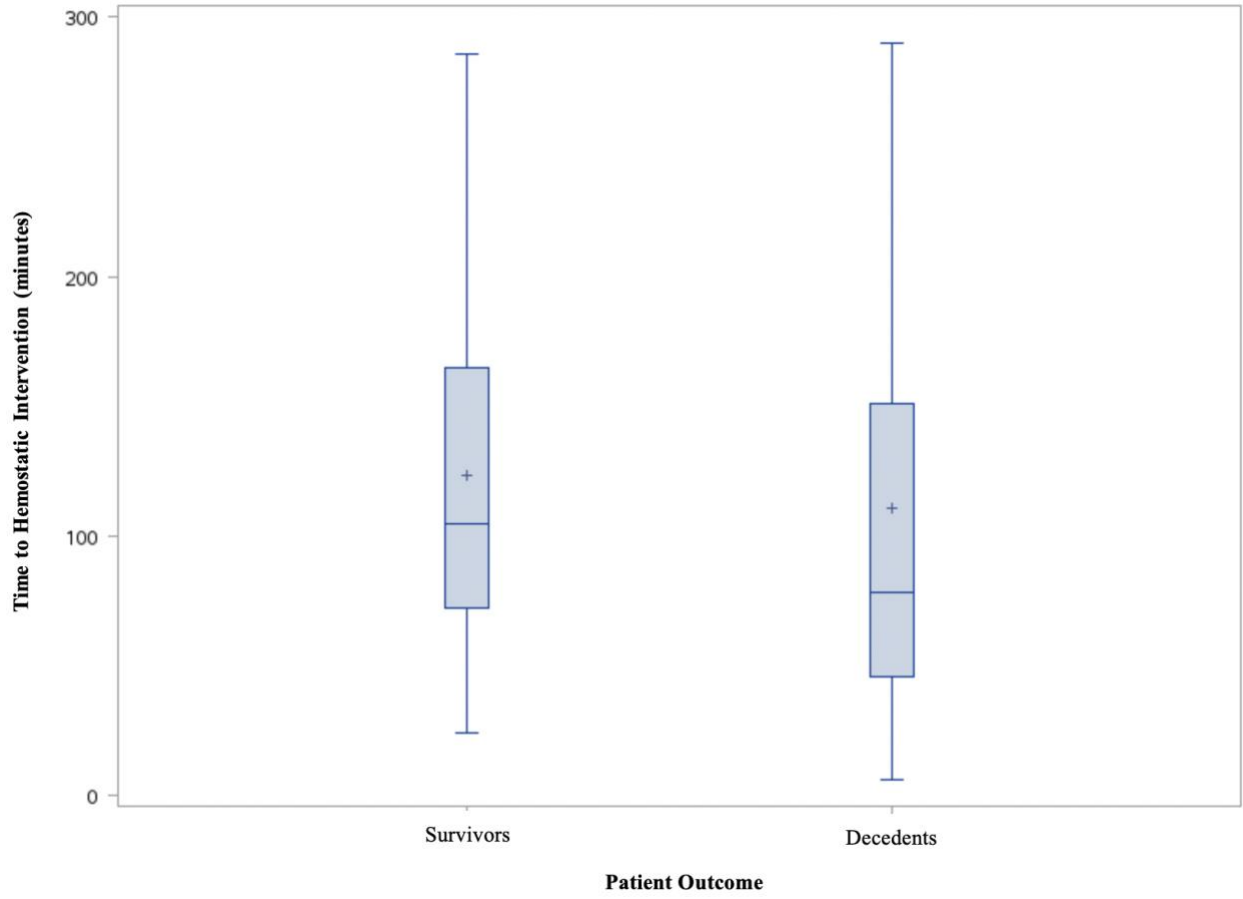
Despite the important limitations, there are important strengths. As discussed above, a recent systematic review identified only two other studies including all bleeding trauma patients rather than specific injury mechanisms or patterns, so our work makes an important contribution to efforts to clarify the impact of time to hemostatic intervention for bleeding trauma patients at large.<sup>13,16,17</sup> Much of the previous literature was also at high risk of bias due to inadequate control of confounding, whereas our methodology accounted for a substantial number of relevant covariates of clinical importance. We also employed clear, clinically relevant definitions of early and delayed hemostasis, which was lacking in many other studies. Further, there was no missing data in our sample, with 100% of included patients having complete, prospective recording of all relevant data. Careful attention was paid to the methodology, with exploration of the need for consideration of time-dependent variables, lack of which is a frequent source of bias.<sup>24</sup> However, because the primary outcome and exposure of interest generally occurred in close temporal association to one another, time-dependent variables could not be incorporated into our model. However, we were able to avoid falsely attributing the time to intervention to the overall period of survival in our analysis. Previous studies have not specifically noted this, and failing to code these variables appropriately may attenuate the beta coefficient, understating any detrimental impact of delay.<sup>24</sup>

For the ultimate clinical implications of delayed hemostasis to be determined, additional studies will be required. Specifically, efforts are underway to conduct a similar study with a larger sample size and including patients from multiple institutions, including at least one high volume United States trauma centre. This will allow a more representative sample to be investigated, and given the high volume of penetrating injuries in the United States, will likely include a multitude of patients undergoing hemostasis within one to two hours, where the impacts of time to intervention across a more homogeneous sample are best explored. The ultimate goal will be to inform future prospective studies investigating more specific time points, including time from injury to achievement of hemostasis on a minute-by-minute basis, as emergency department arrival and start of hemostatic intervention are surrogate markers. Such research will allow for creation of targets analogous to “door-to-balloon” times in cardiology and a more nuanced approach to time management in emergent interventions.<sup>25</sup>

In conclusion, this study failed to demonstrate a statistically significant association between increasing time to intervention and mortality or receipt of pRBCs. These results conflict with the clinical understanding of the pathophysiology of bleeding, and are likely due to sample size limitations, incomplete control of confounding despite inclusion of important variables, and confounding by indication. There remains a need for larger studies and objective characterization of the impact of time to hemostatic intervention on mortality and blood transfusion requirements beyond the idea of the “golden hour”, such that targeted, evidence-informed interventions can be implemented at the clinical and systems levels to reduce mortality in trauma patients as a whole.



**Figure 1.** Identification of Included Patient Cohort from The Ottawa Hospital Trauma Registry.



**Figure 2.** Difference in Time to Hemostatic Intervention Between Decedents and Survivors.

**Table 1.** Characteristics of Patients Undergoing Hemostatic Intervention Within or Beyond 60 minutes of Arrival to Hospital.

|                                | <b>All Patients<br/>(n=147)</b> | <b>Time &lt; 60 min.<br/>(n=24)</b> | <b>Time ≥ 60 min.<br/>(n=123)</b> | <b>p Value</b> |
|--------------------------------|---------------------------------|-------------------------------------|-----------------------------------|----------------|
| Age (Years)                    | 36.0 [27.0-56.0]                | 35.5 [27.5-49.5]                    | 36.0 [27.0-56.0]                  | 0.92           |
| Male Sex                       | 114 (77.6%)                     | 22 (91.7%)                          | 92 (74.8%)                        | 0.11           |
| Mechanism of Injury            |                                 |                                     |                                   | <0.0001        |
| Blunt                          | 74 (50.3%)                      | 2 (8.3%)                            | 72 (58.5%)                        |                |
| Penetrating                    | 73 (49.7%)                      | 22 (91.7%)                          | 51 (41.5%)                        |                |
| Injury Severity Score (ISS)    | 22.0 [13.0-33.0]                | 19.5 [17.0-26.0]                    | 25.0 [11.0-34.0]                  | 0.43           |
| Heart Rate (Beats per Minute)  | 100.0 (28.9)                    | 99.3 (45.3)                         | 100.1 (24.8)                      | 0.69           |
| Systolic Blood Pressure (mmHg) | 120.0 [103.0-146.0]             | 117.0 [107.5-147.0]                 | 120.0 [102.0-145.0]               | 0.95           |
| Glasgow Coma Scale             | 15 [11-15]                      | 13 [7.5-14.5]                       | 15 [13-15]                        | 0.002          |
| Intervention                   |                                 |                                     |                                   | 0.13           |
| Surgery                        | 123 (83.7%)                     | 23 (95.8%)                          | 100 (81.3%)                       |                |
| Angioembolization              | 24 (16.3%)                      | 1 (4.2%)                            | 23 (18.7%)                        |                |
| Time to Intervention (Minutes) | 102.0 [69.0-165.0]              | 42.0 [32.0-51.5]                    | 117.0 [88.0-180.0]                | <0.0001        |
| Length of Stay (Days)          | 9.0 [4.0-21.0]                  | 7.0 [1.2-19.0]                      | 9.0 [4.0-21.0]                    | 0.44           |
| ICU Length of Stay (Days)      | 1.0 [0.0-4.0]                   | 1.0 [0.0-3.5]                       | 1.0 [0.0-5.0]                     | 0.14           |

Data are expressed as median [IQR] or mean (SD) for continuous variables and number of patients (%) for categorical variables. Mann-Whitney *U* tests were used to compare differences between continuous variables and Fisher's exact tests were used to compare differences between categorical variables. *IQR* interquartile range, *SD* standard deviation, *ICU* intensive care unit.

**Table 2.** Multivariable Cox Proportional Hazards Regression Model for Time to Intervention and Mortality (n=147).

|   | <b>aHR (95%CI)</b> | <b>p Value</b> |
|---|--------------------|----------------|
| Time to Hemostatic Intervention (Minutes)   | 0.99 (0.99-1.01)   | 0.10           |
| Mechanism of Injury (Penetrating vs. Blunt) | 0.49 (0.11-2.13)   | 0.34           |
| Age (Years)                                 | 1.02 (0.99-1.04)   | 0.23           |
| Injury Severity Score (ISS)                 | 0.98 (0.93-1.03)   | 0.40           |
| Heart Rate (Beats per Minute)               | 1.00 (0.98-1.01)   | 0.69           |
| Systolic Blood Pressure (mmHg)              | 0.98 (0.97-0.99)   | <0.001         |
| Glasgow Coma Scale (GCS)                    | 0.74 (0.66-0.83)   | <0.0001        |

Adjusted hazard ratio (aHR) and 95% confidence interval (CI) are presented.

**Table 3.** Multivariable Linear Regression Model for Volume of pRBCs Received (n=147).

|   | <b><math>\beta</math> (95%CI)</b> | <b>p Value</b> |
|---|-----------------------------------|----------------|
| $\geq 60$ min. vs. 0-59 min.                | -582.04 (-1,856.52 - 692.43)      | 0.37           |
| Mechanism of Injury (Penetrating vs. Blunt) | -122.56 (-1,323.86 - 1,078.74)    | 0.84           |
| Age (Years)                                 | -3.84 (-29.13 - 21.45)            | 0.76           |
| Injury Severity Score (ISS)                 | 83.69 (43.30 - 124.07)            | <0.0001        |
| Heart Rate (Beats per Minute)               | 8.41 (-6.82 - 23.64)              | 0.28           |
| Systolic Blood Pressure (mmHg)              | -15.46 (-27.96 - -2.95)           | 0.02           |

Parameter estimates ( $\beta$ ) and 95% confidence interval (CI) are presented.

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## **Chapter V – Discussion**

### **5.1 Thesis Summary**

The overall aim of the thesis was to evaluate the current understanding of the objective impact of increasing time to hemostatic intervention in trauma and to determine whether an evidence-informed definition of delayed intervention is supported by the literature. Chapter 2 reviewed the importance of timely identification of traumatic hemorrhage and underscored the reality of clinical and personnel factors contributing to delays in care. Compounding these concerns, classically described signs of significant bleeding are of questionable utility and may oversimplify the course of deterioration of critically ill trauma patients. Despite these concerns, the literature investigating delayed intervention in trauma is heterogenous with respect to patients considered and methodological rigour. To investigate this further, Chapter 3 contained a systematic review and narrative synthesis of the relevant literature, which illustrated that an evidence-informed definition of delayed hemostatic intervention has not been solidified. Further, despite the dogma of the “golden hour”, studies have examined diverse patient populations, injuries, and times of interest from which it is difficult to draw definitive conclusions. The review highlights the need for additional research with more rigorous control of confounding and standardization of eligibility. Finally, Chapter 4 examined a representative cohort of bleeding trauma patients from a Level I trauma centre, which failed to demonstrate a statistically significant association between increased time to hemostatic intervention and mortality or receipt of blood products. While the conclusions are limited by sample size and incomplete control of confounding, this study characterizes a methodologically appropriate way to investigate the associations between increased time to hemostasis and relevant outcomes and will benefit from future efforts to increase sample size.

## 5.2 Importance of Findings

The assessment of the literature supporting the undertaking of the thesis clearly identified the paucity of reliable studies investigating the impact of delays and increasing time to hemostasis on bleeding trauma patients. Given the observation that previous studies in this area focused on a variety of injury patterns, patient populations, and interventions, it was clear that a consolidation of the literature was an essential first step towards developing an understanding of the research to date. Indeed, the included systematic review has allowed for a clear cataloguing and appraisal of previous research efforts, allowing clinicians and researchers alike to reflect on current practices and more adequately question their foundation.

The demonstration that the prevailing dogma of the “golden hour” was developed forty years ago with little supporting evidence, coupled with the finding that an evidence-informed definition of delayed hemostatic intervention has yet to be solidified, provide further impetus to move beyond the notion that “faster is better”. The development of more robust statistical techniques, more advanced trauma care, and more geographically concentrated populations demands that the trauma community as a whole abandons intuition alone, and the included systematic review lays bare the lack of evidence currently informing practice.

The included cohort study serves as an example of the statistical rigour that should guide further research in this realm. While limited by confounding and sample size considerations, it is an important step towards objectively elucidating the clinical implications of increasing time to hemostatic intervention. The study shows that it is feasible to obtain granular time-to-event data in a population of trauma patients, and to appropriately analyze said data with proportional hazards regression. This work can be used as a foundation for additional research efforts, with

the ultimate goal of establishing evidence-based targets for achieving hemostasis, as has been the case with cardiac catheterization and “door-to-balloon times”.

While the thesis work considers specifically time from hospital arrival to hemostasis, the implications extend far beyond that. Over 40% of trauma patients presenting to The Ottawa Hospital are transferred from other centres, and over 20% of Canadians live greater than 60 minutes away from a trauma centre. More focused studies are needed to specifically examine patients presenting to non-trauma centres and collect the data needed to include them in larger cohorts, as well as to avoid contributing further to the biases and shortcomings that can plague healthcare delivery in rural and remote communities. A clearer understanding of the pathophysiology and management of traumatic hemorrhage is also essential for appropriate urban planning and prehospital protocols, as well as streamlining access to care and sharing of resources within the hospital itself. Ultimately, the thesis work represents the early stages of a research program which intends to identify realistic and attainable targets to inform efficient, streamlined surgical and interventional radiological care in order to reduce morbidity and mortality for bleeding trauma patients locally and at large.

### **5.3 Strengths and Limitations**

The thesis work has a number of important strengths. Firstly, the included systematic review represents the only identified synthesis of the literature investigating the impact of increasing time to hemostasis among bleeding trauma patients. A number of studies have investigated time from injury to hospital arrival among all trauma patients, but the examination of the subpopulation of patients specifically requiring hemostatic intervention is an important addition to the literature. Additionally, the systematic review employed a deliberately broad search strategy, developed with the assistance of a library information specialist, to minimize the

likelihood that any potentially relevant works would not be excluded before their abstracts were reviewed. The co-primary outcomes of the systematic review are also a strength, as they allowed the thesis to explore and describe both the objective findings with respect to the impact of increasing time to hemostasis on clinical outcomes, as well as definitions of delay that have been proposed on a more subjective or arbitrary basis.

The cohort study joins a relatively small body of literature investigating time to hemostasis in a broad group of bleeding trauma patients, with only two previous studies employing similar inclusion criteria. As demonstrated in the systematic review, much of the existing literature is at high risk of bias, whereas the included cohort study had rather rigorous control of confounding, adjusting for mechanism of injury, age, ISS, vital signs, and GCS. These are many of the critical factors affecting outcomes in bleeding trauma patients, and adequately capturing this data for a large cohort is a significant strength. As a whole, the thesis was uniquely poised to re-evaluate the current understanding of delayed hemostasis in trauma, presenting a comprehensive assessment of the literature to date and making efforts to address the identified gaps with complete, rigorously controlled, representative, and appropriately analyzed data.

Despite these strengths, there are notable limitations. The systematic review presented a narrative synthesis rather than a meta-analysis and was unable to evaluate other important outcomes, such as missed injuries or unnecessary interventions. However, it must be noted that this is a reflection of the literature itself, which does not contain adequate data to facilitate meta-analysis or evaluation of other outcomes in a methodologically appropriate manner. Despite appropriate statistical analysis and consideration of a number of important confounders, the results of the cohort study were not directly supportive of current understanding and previous studies. This is likely a consequence of residual confounding by indication, as the patients

undergoing the most rapid hemostasis are often the most critically ill. In Chapter 2, we reviewed that the progression towards mortality in bleeding trauma patients may be nonlinear, and in Chapter 4, we discussed that ISS is not necessarily the most accurate descriptor of injury severity, particularly in penetrating injuries.

Importantly, the thesis generally included patients with head injuries as long as they were not felt to be nonsurvivable at the time of presentation, based on the contemporaneous opinion of neurosurgery team as documented in the medical record. The outcomes of interest included all-cause, in-hospital mortality in order to account for the fact that not all patients who present with bleeding injuries die due to bleeding, and that delays to hemostasis can contribute to other causes of death through a variety of physiologic and systems-level mechanisms. These factors, coupled with the observation that GCS was significantly lower in the early hemostasis group, suggest that deaths due to head injuries may have contributed to the increased overall mortality in this group. Overall, despite the methodological rigor of the thesis, the research program as a whole will require additional research to meet its ultimate goals.

#### **5.4 Future Directions**

As outlined above, many of the limitations of the thesis stem from either the nature of the literature as a whole or from residual confounding and a relatively small sample size. The research group has plans to address this with an expansion of the retrospective cohort study in partnership with high volume Canadian and American level I trauma centers. This will allow a larger sample to be considered, and importantly, is likely to increase the number of patients undergoing rapid hemostatic intervention (i.e. within 60 minutes). With a larger sample size, it may prove useful to narrow the inclusion criteria in terms of maximal time to hemostasis, which may mitigate some of the confounding by indication. Ultimately, continuing the thesis work with

a larger, multi-centre study will allow for characterization of the objective impact of increasing time to hemostatic intervention on mortality, receipt of blood products, and length of stay in hospital. This will be imperative in the quest to establish evidence-informed targets for time to hemostasis, as has been seen in acute cardiac care.

With this in mind, it is important to consider what the ideal study may be in this area of research. From a methodological perspective, a randomized trial would likely provide the most rigorous control of confounding and the highest quality evidence, but randomizing patients to delayed care would not be ethical given our current clinical understanding of the pathophysiology of bleeding. Therefore, a prospective observational cohort study, complete with accurate measurement of time from injury to the moment of hemostasis, a larger sample size and greater number of mortality events, and statistical analysis employing methodology such as propensity score matching, may allow researchers to investigate time to hemostasis in trauma in a more robust fashion. In many ways, this research parallels the investigation of surgical wait times at large, and inspiration can be drawn from studies examining delays to orthopedic surgery and emergency, non-cardiac surgery.<sup>1,2</sup>

## **5.5 Conclusion**

Overall, the thesis has demonstrated that despite the prevailing dogma of the “golden hour”, current trauma practice is not necessarily informed by appropriate evidence. The true impact of increasing time to intervention on clinical outcomes is incompletely explored, and a reliable definition of delayed intervention does not yet exist. The included cohort study did not demonstrate a statistically significant association between time to intervention and mortality or receipt of blood products, but represents an important preliminary step in a research program seeking to improve the efficiency and quality of trauma care locally and beyond.

## 5.6 References

1. HIP ATTACK Investigators. Accelerated surgery versus standard care in hip fracture (HIP ATTACK): an international, randomised, controlled trial. *Lancet (London, England)*. 2020;395(10225):698-708. DOI: 10.1016/S0140-6736(20)30058-1.
2. McIsaac DI, Abdulla K, Yang H, Sundaresan S, Doering P, Vaswani SG, Thavorn K, Forster AJ. Association of delay of urgent or emergency surgery with mortality and use of health care resources: a propensity score-matched observational cohort study. *CMAJ*. 2017;189(27):E905-E912. DOI: 10.1503/cmaj.160576.

## **Appendices**

### **Appendix A – Systematic Review Protocol**

#### **Methodology**

The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist has been used as a guide for the design and reporting of our protocol<sup>1</sup>. The review will be registered on PROSPERO (international prospective register of systematic reviews).

#### ***Eligibility Criteria***

The population of interest will include adult patients presenting to hospital with blunt or penetrating injuries to the neck, thorax, abdomen, pelvis, or extremities and who require major hemostatic intervention for bleeding, including surgery or angioembolization, or a combination thereof. Isolated head injuries, burns, electrocutions, and drownings, as well as other non-hemorrhagic mechanisms of injury will be excluded. Studies seeking to define “delayed intervention” for hemostasis, as well as those comparing patients undergoing “delayed” interventions to those without delay or comparing time to intervention, will be eligible, regardless of the definition of delay employed. Outcomes of interest will include the employed definitions of “delayed intervention”, mortality, length of stay in hospital and in ICU, and units of packed red blood cells (pRBCs) transfused. Randomized controlled trials (RCTs; open label, single blind, double blind), case-control studies, and observational cohort (retrospective or prospective) studies will be eligible, though given the nature of the exposure of interest, randomized trials are not anticipated due to ethical concerns with intentionally delaying care. Case series with fewer than five patients, case reports, and commentaries will not be included.

Reference lists of systematic reviews and meta-analyses will be reviewed to identify relevant studies for inclusion.

As there exists significant variation in the management of pediatric trauma, the population of interest will be limited to adults. However, older teenagers may be managed in adult trauma centres and thus may be included in cohorts of adult patients, so studies reporting data on patients aged  $\geq 16$  will also be eligible. Studies will also remain eligible in the event that a small (<5%) proportion of the total population consists of pediatric patients.

Studies will be included irrespective of the specified follow-up period or setting. Study inclusion will be restricted to English and French languages and to peer-reviewed publications. No restrictions will be placed on publication year or study size, with the exception of case series with fewer than five patients, as outlined above. Conference abstracts and grey literature will be eligible for inclusion provided these information sources otherwise meet the specified inclusion criteria. Inclusion and exclusion criteria will be implemented using a standardized study inclusion form. Study eligibility will be assessed in duplicate.

#### *Information Sources and Search Strategy*

The search strategy will be developed with the assistance of a qualified library information specialist. EMBASE, MEDLINE, and Web of Science will be incorporated in the search. No restrictions with respect to date or language will be applied to the initial search. Reference lists of included studies, as well as those of relevant systematic reviews, will be reviewed to identify potentially relevant citations.

In the event that potentially eligible data is identified in abstract or is incompletely published, attempts will be made to seek clarification and obtain complete data from the corresponding author. Clinicaltrials.gov will also be checked for any additional studies that fit

this review's inclusion criteria but that were not captured by our search strategy. A combination of medical subject headings (MeSH terms) and text words detailing the population and intervention of interest will be used for the search strategy. Duplicate citations will be removed.

### *Study Records*

### *Data Management*

A list of abstracts to be screened will be maintained online using Covidence® software, including results of reviewer agreement during abstract screening. A backup copy of the search strategy (.doc format) and the resulting abstract list (.txt format) will be maintained on a physical hard drive by one of the study authors (T.L.). Covidence® software will be used to maintain a list of full-text studies included following initial abstract screening. Full text articles in PDF format will be maintained in a shared folder on a physical hard drive by one of the study authors (T.L.). Full text review for inclusion will be completed using Covidence®, including reasons for full-text exclusion. Data abstraction will be performed using Covidence for study characteristics and an Excel® abstraction database for outcome data, which will be stored on a physical hard drive of one of the authors (T.L.).

### *Selection Process*

Titles and abstracts will be reviewed in duplicate by two independent reviewers using Covidence® software (Melbourne, Australia). Potentially eligible full texts carried forward following abstract screening will be reviewed in duplicate by two independent reviewers. Disagreements with respect to abstract and full-text screening will be resolved by consensus, or by a third senior author when consensus cannot be reached. Study eligibility criteria (Table 1) will be applied using an electronic eligibility checklist via Covidence®.

Abstract and full text screening will be performed by dividing the list of potentially eligible abstracts and full-text articles among the authors, with duplicated coverage of all abstract screening/full-text review. The results of abstract screening and full text study selection will be documented and reported using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram<sup>2</sup>.

#### Data Collection Process

Data collection with respect to study characteristics, population characteristics, information surrounding intervention/comparator, and funding will be conducted using an electronic data capture form via Covidence<sup>®</sup>. Outcome data and event rates will be captured using an Excel<sup>®</sup> database. The data capture process will be piloted by two reviewers by applying the data collection process to two full-text articles and modifying the abstraction form as required following the piloting process. All data collection will be performed independently and in duplicate using Covidence<sup>®</sup> and Excel<sup>®</sup>. Discrepancies with respect to abstracted data will be resolved by consensus or by a third senior author when required.

#### Data Items

Data will be collected on study characteristics, sample characteristics (e.g. demographic data, mechanism of injury, Injury Severity Score [ISS], etc.), interventions and comparators (e.g. time to intervention [as either continuous or categorical variable], hemostatic interventions received [e.g. surgery or angioembolization, nature of procedure, etc.]), and outcomes of interest (Table 2). If effect sizes cannot be determined based on the data provided, attempts will be made to contact authors for clarification and additional data. pRBC transfusions reported in volume (mL) will be converted to units by dividing by 300<sup>3</sup>. Hematocrit (%) will be converted to hemoglobin (g/dL) by dividing by 3<sup>3</sup>.

## *Outcomes*

### *Primary Outcome*

The primary outcome will be the temporal definition of delayed intervention employed in the identified studies. The dogma in trauma care has long been that definitive care must be delivered in the “golden hour”, representing the initial 60 minutes following injury<sup>4</sup>. However, this was first presented in the 1970s and 1980s with little supporting evidence, and there have been substantial changes to trauma care in the subsequent fifty years. Therefore, it is believed to be of great importance to survey the literature for more modern definitions of delayed intervention.

### *Secondary Outcomes*

1. Overall Mortality: The primary goal of hemostatic intervention in trauma is to control bleeding in order to prevent mortality. Use of overall mortality as a secondary outcome serves as a conservative measure of death and will therefore avoid events that may be missed with a more selective outcome measure (e.g. death from bleeding).
2. Units of pRBCs Transfused: Transfusion of blood products is an indirect measure of bleeding, and the volume of blood products transfused is expected to increase as more resuscitation is required. Therefore, longer time to hemostatic intervention may result in a greater need for transfusion, making it an important outcome. Further, there are risks associated with receipt of blood products, including infection, lung injury, and volume overload, so any efforts to reduce need for transfusion should be pursued.
3. Length of Stay in Hospital and in ICU: Length of stay, both in hospital and in the ICU, is a measure of injury severity and degree of resuscitation needed. Delayed hemostatic intervention may create a need for more aggressive resuscitation and therefore increased

length of stay. Importantly, hospital-based care, and particularly critical care, is associated with significant costs to the public healthcare system. Consequently, any intervention that can reduce length of stay in hospital is of critical importance for the system as a whole.

### *Risk of Bias in Individual Studies*

The risk of bias for each included study will be assessed in duplicate by independent reviewers in an unblinded fashion. Any disagreements will be resolved through consensus or a third senior author. RCTs will be assessed using the Cochrane Handbook ‘Risk of Bias 2’ (RoB2) assessment tool<sup>5</sup>. The Risk Of Bias In Non-Randomized Studies of Interventions (ROBINS-I) tool will be used to assess potential bias in included observational cohort studies<sup>6</sup>. The potential impact of bias as assessed with the RoB2 and ROBINS-I tools will be considered for any meta-analyses conducted. A-priori-defined confounders are listed in Table 2.

### *Data Synthesis*

Important characteristics of the included studies will be presented in tables as well as incorporated into a narrative synthesis, which will be grouped by the outcomes of interest. The outcomes of interest are expected to be reported as either dichotomous (e.g. delayed or not delayed) or time-to-event measures. Summary measures for dichotomous outcomes will include odds ratios or risk ratios with associated 95% confidence intervals, while hazard ratios with associated 95% confidence intervals will be extracted from individual studies or calculated from the available data for time-to-event measures<sup>7</sup>. Forest plots will be used to present the outcomes of individual studies with their corresponding 95% confidence intervals as well as the pooled estimate of effect across all studies with the corresponding 95% confidence interval.

The heterogeneity of patient populations, interventions, reported outcomes, and follow-up timeframes of included studies will be reviewed by all authors to determine whether a meta-analysis will be both feasible and appropriate. A random-effects model will be used to perform the meta-analysis, as it will provide a more conservative estimate than a fixed-effects model. The heterogeneity of effect sizes across included studies will be examined using the Cochrane Q and the  $I^2$  statistics. We will use categories of low (0-30%), moderate (31-60%), and substantial (61-100%) to interpret the  $I^2$  statistic<sup>8</sup>.

#### *Planned Sensitivity and Subgroup Analyses*

Planned subgroup analyses include stratifying patients by blunt versus penetrating injury, surgical versus radiological procedure, concomitant head injury, location of bleeding injury (e.g. liver, spleen, extremity, etc.), and ISS. Sensitivity analyses of studies judged to be at low risk of bias will be performed.

#### *Meta-Biases*

Abstracts without full-text publications will be considered for inclusion as long as they otherwise meet inclusion criteria and report at least one outcome of interest, in an effort to reduce publication bias. Additionally, funnel plots and Egger's regression tests will be employed to identify publication and small sample bias if greater than ten studies are included. Efforts will be made to contact study authors to obtain any missing data. Random-effects models will be used to mitigate the possibility of small sample bias.

#### *Confidence in Cumulative Evidence*

The GRADE approach will be used to rate the quality of evidence of estimates derived from each meta-analysis, and results will be presented alongside a GRADE assessment in a table<sup>9</sup>.

**Table 1. Eligibility Criteria**

| Study Parameter  | Criteria for Inclusion   |
|--|--|
| <u>P</u> opulation                                       | <ul style="list-style-type: none"> <li><input type="checkbox"/> Adult patients (<math>\geq 16</math> years of age)               <ul style="list-style-type: none"> <li><input type="checkbox"/> Studies will remain eligible for inclusion if data on adolescent patients aged <math>\geq 16</math> years of age are included within the same cohort as adult patients.</li> <li><input type="checkbox"/> Studies will remain eligible if a mixed age population is reported, provided pediatric patients constitute <math>&lt; 5\%</math> of the total study population.</li> </ul> </li> <li><input type="checkbox"/> Admitted with blunt or penetrating injuries to the neck, thorax, abdomen, pelvis, or extremities and requiring major hemostatic intervention for bleeding (surgery and/or angioembolization)</li> </ul> |
| <u>I</u> ntervention                                     | <ul style="list-style-type: none"> <li><input type="checkbox"/> “Delayed intervention” for hemostasis and/or increased time to hemostatic intervention</li> </ul>  |
| <u>C</u> omparator                                       | <ul style="list-style-type: none"> <li><input type="checkbox"/> No “delayed intervention” for hemostasis</li> </ul>  |
| Primary <u>O</u> utcome                                  | <ul style="list-style-type: none"> <li><input type="checkbox"/> Temporal definition of “delayed intervention” employed</li> </ul>  |
| Secondary <u>O</u> utcomes                               | <ul style="list-style-type: none"> <li><input type="checkbox"/> Overall mortality</li> <li><input type="checkbox"/> Units of pRBC transfused</li> <li><input type="checkbox"/> Length of stay in hospital and ICU</li> </ul>   |
| pRBC = packed red blood cells; ICU = intensive care unit |  |

**Table 2. Data Items**

|                                     |   |
|-------------------------------------|---|
| <p><b>Study Characteristics</b></p> | <ul style="list-style-type: none"> <li><input type="checkbox"/> Title</li> <li><input type="checkbox"/> First author</li> <li><input type="checkbox"/> Year of publication</li> <li><input type="checkbox"/> Publication status</li> <li><input type="checkbox"/> Journal</li> <li><input type="checkbox"/> Full reference information + PMID</li> <li><input type="checkbox"/> Country of corresponding author</li> <li><input type="checkbox"/> Study design             <ul style="list-style-type: none"> <li><input type="checkbox"/> RCT                 <ul style="list-style-type: none"> <li><input type="checkbox"/> Blinding (open, single, double)</li> </ul> </li> <li><input type="checkbox"/> Observational                 <ul style="list-style-type: none"> <li><input type="checkbox"/> Cohort/Case-Control</li> <li><input type="checkbox"/> Prospective/Retrospective</li> </ul> </li> </ul> </li> <li><input type="checkbox"/> Number of participants</li> <li><input type="checkbox"/> Duration of follow-up</li> </ul>  |
| <p><b>Population</b></p>            | <ul style="list-style-type: none"> <li><input type="checkbox"/> Demographic characteristics             <ul style="list-style-type: none"> <li><input type="checkbox"/> Age (C)</li> <li><input type="checkbox"/> Interfacility transfer/direct from scene (C)</li> <li><input type="checkbox"/> Male/female proportions</li> </ul> </li> <li><input type="checkbox"/> Injury characteristics             <ul style="list-style-type: none"> <li><input type="checkbox"/> Mechanism of injury (C)</li> <li><input type="checkbox"/> Injured organ (liver, spleen, kidney, heart, lung, extremity, neck, etc.) (C)</li> <li><input type="checkbox"/> Injury Severity Score (ISS) score (C)</li> <li><input type="checkbox"/> AAST injury scoring grade (where appropriate; C)</li> <li><input type="checkbox"/> Concurrent head injury (C)</li> </ul> </li> <li><input type="checkbox"/> Clinical characteristics             <ul style="list-style-type: none"> <li><input type="checkbox"/> Heart rate (C)</li> <li><input type="checkbox"/> Systolic blood pressure (C)</li> <li><input type="checkbox"/> Lactate (C)</li> <li><input type="checkbox"/> Blood gas values (C)</li> <li><input type="checkbox"/> Hemoglobin level and change over time (C)</li> <li><input type="checkbox"/> FAST results (C)</li> <li><input type="checkbox"/> Use of adjuvant hemostatic products (e.g. tranexamic acid) (C)</li> </ul> </li> </ul> |

|                                |   |
|--------------------------------|---|
|                                | <ul style="list-style-type: none"> <li><input type="checkbox"/> Presence of active extravasation on initial imaging (C)</li> <li><input type="checkbox"/> Location of hemostatic procedure (operating room, emergency department, interventional radiology; C)</li> </ul>   |
| <b>Intervention/Comparator</b> | <ul style="list-style-type: none"> <li><input type="checkbox"/> “Delayed intervention” for hemostasis (regardless of definition)</li> <li><input type="checkbox"/> Increased time to hemostatic intervention (continuous or categorical)</li> </ul>   |
| <b>Outcomes</b>                | <ul style="list-style-type: none"> <li><input type="checkbox"/> Temporal definition of “delayed intervention” employed (in minutes, hours, etc.)</li> <li><input type="checkbox"/> Overall mortality <ul style="list-style-type: none"> <li><input type="checkbox"/> Mortality due to bleeding</li> </ul> </li> <li><input type="checkbox"/> Units of pRBC transfused</li> <li><input type="checkbox"/> Length of stay in hospital and ICU</li> </ul> |
| <b>Funding/Disclosures</b>     | <ul style="list-style-type: none"> <li><input type="checkbox"/> Granting agencies</li> <li><input type="checkbox"/> Grant identification numbers</li> <li><input type="checkbox"/> Relevant disclosures (i.e. consulting fees, honoraria, equity ownership).</li> </ul>   |

\*(C) indicates confounder of interest.

FAST = focused assessment with sonography in trauma; pRBC = packed red blood cells; ICU = intensive care unit

## References

1. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA, Group P-P. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev.* 2015;4(1):1. DOI: 10.1186/2046-4053-4-1.
2. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med.* 2009;6(7). DOI: 10.1371/journal.pmed.1000100.
3. Elzik ME, Dirschl DR, Dahners LE. Correlation of transfusion volume to change in hematocrit. *Am J Hematol.* 2006;81(2):145-146. DOI: 10.1002/ajh.20517.
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5. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng H-Y, Corbett MS, Eldridge SM, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ.* 2019;366:l4898. DOI: 10.1136/bmj.l4898.
6. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ.* 2016;355:i4919. DOI: 10.1136/bmj.i4919.
7. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials.* 2007;8:16. DOI: 10.1186/1745-6215-8-16.

8. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ WV. Cochrane Handbook for Systematic Reviews of Interventions Version 6.2. *Cochrane*. 2021. [www.training.cochrane.org/handbook](http://www.training.cochrane.org/handbook).
9. GRADEpro GDT: GRADEpro Guideline Development Tool. 2020.

## Appendix B – Systematic Review Search Strategy

Database: Embase Classic+Embase <1947 to 2022 January 25>, Ovid MEDLINE(R) ALL <1946 to January 25, 2022>

Search Strategy:

- 
- 1 (trauma\* or polytrauma\* or injur\* or operation).ti. (1140962)
  - 2 ("time to" or delay or timing).ti. (695033)
  - 3 ("time to" or delay or timing).ab. (8650830)
  - 4 or/2-3 (8889545)
  - 5 (hemosta\* or surgery or operat\* or angio\* or emboliz\* or laparotom\* or procedure).ti. (1878704)
  - 6 (hemosta\* or surgery or operat\* or angio\* or emboliz\* or laparotom\* or procedure).ab. (7251042)
  - 7 or/5-6 (7922223)
  - 8 (predict\* or model\* or risk\* or associat\* or factor\* or effect\* or affect\* or defin\* or impact\*).ti. (12272191)
  - 9 (mortality or survival).ab. (4289831)
  - 10 1 and 4 and 7 and 8 and 9 (3106)
  - 11 exp animals/ not humans/ (17884988)
  - 12 10 not 11 (1989)

## Appendix C – Systematic Review PRISMA Checklist

| Section and Topic             | Item # | Checklist item   | Location where item is reported |
|-------------------------------|--------|--|---------------------------------|
| <b>TITLE</b>                  |        |  |                                 |
| Title                         | 1      | Identify the report as a systematic review.  | Title Page                      |
| <b>ABSTRACT</b>               |        |  |                                 |
| Abstract                      | 2      | See the PRISMA 2020 for Abstracts checklist.   | Abstract                        |
| <b>INTRODUCTION</b>           |        |  |                                 |
| Rationale                     | 3      | Describe the rationale for the review in the context of existing knowledge.  | 1-2                             |
| Objectives                    | 4      | Provide an explicit statement of the objective(s) or question(s) the review addresses.   | 2                               |
| <b>METHODS</b>                |        |  |                                 |
| Eligibility criteria          | 5      | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.  | 2-3                             |
| Information sources           | 6      | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.  | 3                               |
| Search strategy               | 7      | Present the full search strategies for all databases, registers and websites, including any filters and limits used.   | Appendix A                      |
| Selection process             | 8      | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.                     | 3                               |
| Data collection process       | 9      | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | 3                               |
| Data items                    | 10a    | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.                        | 4                               |
|                               | 10b    | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.   | Protocol                        |
| Study risk of bias assessment | 11     | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.                                    | 3-4                             |
| Effect measures               | 12     | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.  | 4                               |

|                               |     |  |             |
|-------------------------------|-----|--|-------------|
| Synthesis methods             | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).   | 4           |
|                               | 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.  | 4, Protocol |
|                               | 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses.   | 4, Protocol |
|                               | 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.                          | 4, Protocol |
|                               | 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).   | Protocol    |
|                               | 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results.   | Protocol    |
| Reporting bias assessment     | 14  | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).  | 3, Figure 2 |
| Certainty assessment          | 15  | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.  | Protocol    |
| <b>RESULTS</b>                |     |  |             |
| Study selection               | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.   | 4, Figure 1 |
|                               | 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.  | N/A         |
| Study characteristics         | 17  | Cite each included study and present its characteristics.  | 4, Table 1  |
| Risk of bias in studies       | 18  | Present assessments of risk of bias for each included study.   | 5, Figure 2 |
| Results of individual studies | 19  | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.   | Table 2     |
| Results of syntheses          | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.   | N/A         |
|                               | 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | N/A         |
|                               | 20c | Present results of all investigations of possible causes of heterogeneity among study results.   | N/A         |
|                               | 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.   | N/A         |
| Reporting biases              | 21  | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.  | N/A         |

|  |     |  |                          |
|--|-----|--|--------------------------|
| Certainty of evidence                          | 22  | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.  | N/A                      |
| <b>DISCUSSION</b>                              |     |  |                          |
| Discussion                                     | 23a | Provide a general interpretation of the results in the context of other evidence.  | 9-12                     |
|  | 23b | Discuss any limitations of the evidence included in the review.  | 12-13                    |
|  | 23c | Discuss any limitations of the review processes used.  | 12-13                    |
|  | 23d | Discuss implications of the results for practice, policy, and future research.   | 11-13                    |
| <b>OTHER INFORMATION</b>                       |     |  |                          |
| Registration and protocol                      | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered.   | Title Page               |
|  | 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared.   | Title Page               |
|  | 24c | Describe and explain any amendments to information provided at registration or in the protocol.  | Title Page               |
| Support  | 25  | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.  | Title Page               |
| Competing interests                            | 26  | Declare any competing interests of review authors.   | Title Page               |
| Availability of data, code and other materials | 27  | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | Via Corresponding Author |

## Appendix D – Ethics Approval Letter



**Ottawa Health Science Network Research Ethics Board (OHSN-REB) / Conseil  
d'éthique de la recherche du réseau de science de la santé d'Ottawa (CÉR-RSSO)**

**Date:** September 29, 2021  
**Principal Investigator:** Dr. Christian Vaillancourt, TOH/OHRI  
**Protocol ID:** 20210064-01H  
**Study Title:** The Impact of Time to Major Intervention and Delayed Care for Patients with Traumatic Hemorrhage  
**Submission Type:** Initial Application  
**Review Type:** Delegated  
**Date of Approval:** September 29, 2021  
**Approval Expiry Date:** September 29, 2022

Dear Dr. Vaillancourt,

An **Institutional approval (OHRI) letter is required prior to the conduct of the study** at this site. The institutional approval letter is an indication that you have satisfied ethics, contracts, departmental notifications, as applicable.

Thank you for submitting the above referenced study. The Ottawa Health Science Network Research Ethics Board (OHSN-REB) has reviewed the application and granted approval for your study. This approval is granted until the expiration date noted above. This research study is to be conducted by the investigator noted above.

The **OHSN-REB ethics approval** is applicable only for The Ottawa Hospital.

Documents Approved:

| Document Name            | Document Version Date |
|--------------------------|-----------------------|
| <a href="#">Protocol</a> | September 16, 2021    |

No deviations from, or changes to, the protocol should be initiated without prior written approval of an appropriate amendment from the OHSN-REB, except when necessary to eliminate immediate hazard(s) to study participants.

REB members involved in the research project do not participate in the review, discussion or decision.

If the study is to continue beyond the expiry date noted above, a Continuing Review Form must be received by the OHSN-REB on or prior to the full board submission deadline date of the meeting scheduled to occur a minimum of 30 days prior to the study expiry date. If the study has been completed by the expiry noted above, a Study Closure Report must be received by the OHSN-REB.

The OHSN-REB operates in compliance with, and is constituted in accordance with, the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2); Part C, Division 5 of the Food and Drug Regulations; or with the definition in the Interim Order Respecting Clinical Trials for Medical Devices and Drugs Relating to COVID-19; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations; and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. OHSN-REB is qualified through the CTO REB Qualification Program and is registered with the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protection (OHRP).

Please do not hesitate to contact us if you have any questions.

Sincerely,

Francine F.-A. Sarazin, Ph.D.  
Vice Chairperson  
Ottawa Health Science Network Research Ethics Board

/HMc