Evaluating Risk of Delayed Major Bleeding in Critically Ill Trauma Patients

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Abstract

Background:

Up to 40% of trauma patients die during the first 24 hours after injury due to massive hemorrhage. In patients who survive this critical time period, no information is available on rates of delayed major bleeding or factors associated with delayed major bleeding.

Methods:

A retrospective chart review of 150 critically ill adult trauma patients was used to determine the incidence of delayed major bleeding events. Cox proportional hazards multivariate analysis was performed to assess for risk factors associated with delayed major bleeding events. The anticipated rate of delayed major bleeding events was 10%.

Results:

The incidence of delayed major bleeding in this cohort of critically ill trauma patients was 44%. Predictors that were statistically significantly associated with delayed major bleeding included: male gender, pre-injury use of the antiplatelet agents aspirin and/or clopidogrel, presence of intracranial bleeding, higher injury severity scores, requirement of massive transfusion, and low pH values. Use of anticoagulant prophylaxis was not associated with delayed major bleeding.

Conclusion:

The rate of delayed major bleeding was higher than estimated. Larger retrospective and prospective cohorts are needed to confirm these findings.

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List of Abbreviations

AIS	Abbreviated injury scale
APACHE	Acute physiology and chronic health evaluation
ASA	Aspirin
CRF	Case report form
DAI	Diffuse axonal injury
DVT	Deep vein thrombosis
EDH	Epidural hematoma
FFP	Fresh frozen plasma
GCS	Glasgow coma score
GI	Gastrointestinal
Hgb	Hemoglobin
HR	Heart rate
ICH	Intracerebral hemorrhage
ICU	Intensive care unit
INR	International normalized ratio
IQR	Interquartile range
ISS	Injury severity score
IV	Intravenous
IVH	Intraventricular hemorrhage
LMWH	Low molecular weight heparin
MOF	Multi-organ failure
MTP	Massive transfusion protocol
MV	Mechanical ventilation
PE	Pulmonary embolism
Plt	Platelet
pRBC	Packed red blood cells
PT	Prothrombin time
PTT	Partial thromboplastin time
RBC	Red blood cell
RCT	Randomized controlled trial
rFVIIa	Recombinant activated Factor VII
SAH	Subarachnoid hemorrhage
SBP	Systolic blood pressure
SCDs	Sequential compression devices
SD	Standard deviation

SDH	Subdural hematoma
TBI	Traumatic brain injury
TXA	Tranexamic acid
UFH	Unfractionated heparin
VTE	Venous thromboembolism

Introduction

Statement of the Problem

The risk of delayed major bleeding in trauma patients has not been reported in the literature. Patients who are identified to have delayed major bleeding may require delayed initiation (or reinstitution) of antiplatelet agents, anticoagulants (including thromboprophylaxis), and anti-inflammatory drugs. Currently, there are no parameters to guide physicians on when it is safe to start these medications and decisions are based on individual clinician preference and gestalt. Furthermore, identifying patients at greater risk of bleeding may lead to prolonged acute monitoring in the ICU or appropriate step down unit, if ICU treatments are no longer needed. Finally, certain injury patterns, such as solid organ injury, may be identified that are associated with increased delayed bleeding risk and may modify how they are managed (eg. conservative vs. embolization vs. surgical). The purpose of this project was to evaluate the incidence of delayed major bleeding in critically ill trauma patients, and risk factors associated with delayed major bleeding. This data will be incorporated in the development of prospective observational studies in this population.

Background

Trauma is the leading cause of death in persons under the age of 40 years and hemorrhage is responsible for at least 40% of trauma related deaths[1;2] within the first 24 hours following injury, with up to half of patients dying before arriving to hospital. During the last several decades, the focus of research in bleeding trauma patients has been

targeted at understanding pathophysiologic mechanisms for coagulopathy, crystalloid fluid and blood product administration during early post-injury resuscitation, and use of alternative therapies to minimize bleeding and reduce mortality. Civilian and military populations have been extensively evaluated to determine impact of and predictors of massive transfusion and use of antifibrinolytics on all-cause mortality and bleeding related mortality during the first 24 hours of intensive care hospitalization[3,4,5,6,7,8,9]. Clinical characteristics identified to be associated with early death from traumatic bleeding include advanced age, Glasgow Coma Scale (GCS) score, and systolic blood pressure (SBP)[10]. The CRASH-2 study recently demonstrated a significant reduction in all-cause mortality with use of tranexamic acid (TXA) in bleeding trauma patients,[3] with the greatest reduction in mortality observed when TXA is given within three hours of injury[11]. Despite these trials, treatment post-injury is costly and mortality remains high[12].

The focus of research in bleeding trauma patients has been directed at the immediate post-injury period with little emphasis on the potential for delayed hemorrhage in survivors of the first 24 hours. The paucity of information during this time frame in this high risk bleeding group of critically ill multisystem trauma patients indicates a need to evaluate clinical risk factors of delayed hemorrhage.

Trauma Induced Coagulopathy

Trauma induced coagulopathy is common with up to 25% of severely injured patients demonstrating coagulopathy, using conventional coagulation profiles (prothrombin time (PT), partial thromboplastin time (PTT) and platelet counts), upon arrival to trauma

centres[13-15]. In these cohort studies the incidence of coagulopathy increased with severity of injury and the presence of coagulopathy at presentation to hospital was associated with increased mortality of 46% compared to 11% in those with normal clotting parameters. Coagulopathy was also independently associated with increased transfusion requirements, organ injury, infectious complications, and admission to intensive care units[15;16]. Other studies have shown that trauma patients with coagulation abnormalities are more likely to develop organ dysfunction and have longer admissions to the ICU[17]. Clinically, trauma induced coagulopathy is a syndrome of non-surgical bleeding and oozing from mucosa, wounds, and vascular access sites that is distinct from simple massive hemorrhage[18].

While there is no universally accepted definition of trauma induced coagulopathy[16], it has generally been defined as a prolongation of prothrombin time[19]. The advantage of using standard assays such as PT, PTT, and fibrinogen is their widespread availability. PT is felt to be the most sensitive assay to detect multiple coagulation factor deficiencies and a better marker of trauma induced coagulopathy[20]. There are several disadvantages to these lab parameters including a lengthy wait to obtain results. The PT and PTT tests were originally developed to evaluate clotting factor deficiencies, not acquired coagulopathy and are poor predictors of late bleeding in these settings[16].

Coagulopathy after trauma is multifactorial and involves all components of the coagulation system often manifesting in systemic inflammatory response syndrome. Dilution and hypothermia as part of resuscitation efforts were previously felt to contribute directly to coagulopathy, but many other factors have since been identified that interact and worsen coagulopathy in bleeding patients. Tissue damage and

endothelial disruption is the inciting factor resulting in thrombin generation and activation of coagulation, with shock and activation of protein C leading to consumption of coagulation factors and hyperfibrinolysis[21]. This is commonly called the first phase of trauma induced coagulopathy and is a primary response to injury[16;19]. Certain injuries are also associated with coagulopathy, in particular, traumatic brain injury (TBI), due to release of brain-specific thromboplastins into the circulation and consumption of clotting factors[22]. Hyperfibrinolysis has also be shown to increase bleeding in brain injured patients[23]. Retrospective cohort studies have demonstrated an association between higher incidence of coagulopathy with increasing injury severity scores (ISS) resulting in excess in-hospital mortality [13-15]; coagulopathy was measured using routine coagulation parameters mentioned previously, and this finding was also seen in patients with brain injury[13]. The second phase of trauma induced coagulopathy is a result of medical interventions during resuscitation and their consequences, in particular hypothermia, acidosis and hemodilution from resuscitation efforts[16;19]. Lastly, during the post-resuscitation period there is an acute phase response predisposing to prothrombotic state and venous thrombosis[16;19]. While trauma itself is the main cause of trauma induced coagulopathy, resuscitation efforts also contribute to a 'lethal triad' of refractory coagulopathy, hypothermia and metabolic acidosis.

Hypothermia

Hypothermia occurs commonly after trauma and is multifactorial in etiology. Following injury the body is unable to generate heat due to blocked shivering response, altered

central thermoregulation, and reduced cellular metabolic activity[2;24]. Resuscitation fluids and blood products given without warming and surgical procedures leading to prolonged exposure of body cavities also contribute to hypothermic states[2]. The clinical impact of hypothermia is most relevant when core body temperatures fall below 36 degrees Celsius; trauma victims with core temperatures below 35 degrees Celsius have a poor prognosis while those with core temperature of 32 degrees Celsius have 100% mortality[25].

Platelet function and coagulation protease activity are inhibited by hypothermic states with platelets showing the greatest sensitivity due to reduced effect of von Willebrand factor and platelet activation[26]. Hypothermia reduces the rate of enzyme clotting factor activities by 10% for each 1 degree Celsius drop in core body temperature[24]. Although hypothermia is an important contributor to trauma related coagulopathy, it likely has minimal impact on hemostasis given modern resuscitation efforts include both passive and active measures of rewarming[2] and the relatively mild hypothermia (33-36 degrees Celsius) commonly seen in trauma patients[26].

Acidosis

Hypoperfusion from low-flow shock states and excess use of saline resuscitation fluids contribute to acidemia[2]. Prolonged and inadequate tissue perfusion leads to anaerobic cellular metabolism and production of lactate causing a reduction in pH. Abnormally low pH leads to impaired cardiac contractility and vasodilation, further exacerbating the cycle of low-perfusion states and acidosis[2;27].

Both animal and human blood studies have shown adverse effects of acidosis on the coagulation cascade[28;29]. Coagulation function was measured using the PT, PTT, thrombin generation, and platelet counts. Induction of acidosis resulted in 20% prolongation of PT and PTT, and at least 50% reduction in platelet counts, thrombin generation and fibrinogen levels. Plasma protease function decreases linearly with reduction in pH and acidosis also leads to increased degradation of fibrinogen[26;29]. The internal structure and shape of platelets changes in acidotic environments, impairing platelet aggregation[24].

Treatment of acidosis mainly focuses on restoring circulation to improve and maintain tissue perfusion through aerobic metabolism. Use of agents to reverse acidosis such as buffered solutions and sodium bicarbonate have shown improvement in measurement of pH; however, coagulopathy persists as it does not address the cause, and other factors beyond reduced protease activity are effected and may include a negative effect on conversion of fibrinogen to fibrin[26-28]. As with hypothermia, only severe acidosis is likely to impact the coagulation cascade and if present is a marker of the severity of underlying shock state from hypoperfusion[30].

Massive Transfusion and Hemodilution

There are no accurate laboratory studies currently available that effectively evaluate trauma induced coagulopathy. The standard measures are PT, PTT, fibrinogen and platelet count which are widely available but provide limited information about thrombus formation during acute hemorrhage. The current management of trauma induced

coagulopathy supports the use of transfusion protocols to empirically replace blood and clotting factors.

Massive transfusion is defined as transfusion of at least ten units of packed red blood cells (pRBC) over 24 hours in a patient who has severe or uncontrolled bleeding[24;31;32]. Hemodilution results from the shift of interstitial and cellular fluids leading to a deficiency in clotting factors in the plasma[19]; in addition, transfusion of red blood cells and use of crystalloid resuscitation fluids dilute clotting factors and interrupt clot formation[26;33]. Duke et al. retrospectively evaluated restricting the use of crystalloid resuscitation fluids in trauma patients requiring surgery[34]. Limiting the use of intravenous fluids before surgery improved mortality rates, both intra-operatively and overall, compared to patients with standard preoperative fluid resuscitation efforts[34]. The difference in mortality was attributed to dilution of coagulation factors and increase in blood pressure and increased hemorrhage volumes in patients with unrestricted resuscitation. This concept of “permissive hypotension” has been prospectively evaluated in a small randomized trial of trauma patients requiring surgical intervention; patients managed by hypotensive resuscitation with lower blood pressure targets had lower IV fluid and transfusion volumes administered and lower mortality compared to those with standard blood pressure targets[35]. While coagulopathy has been seen in patients receiving little or no intravenous therapy[16], this combination of lowered blood pressure targets during acute resuscitation of trauma patients and limiting dilution effects of crystalloid fluid replacement appears to minimize effects of trauma induced coagulopathy and lower overall mortality.

To ensure a more balanced resuscitation, massive transfusion protocols (MTP) have been developed. These protocols support greater use of plasma-based products and have shown reduced mortality and rates of organ dysfunction[36-42]. Unfortunately, there is no standardized ratio of blood products in these packages and the efficacy varies between studies and centres. MTPs may reduce mortality but their activation may be unnecessary as it is difficult to anticipate which patients will benefit from hemostatic resuscitation. Early death in trauma patients can result in higher RBC/FP (frozen plasma) ratio, which may not reflect improved resuscitation but rather can indicate death before FP is available to be transfused[43].

In recent years use of other transfusion products has been evaluated in clinical trials for the management of early trauma associated hemorrhage. Recombinant activated Factor VII (rFVIIa) was assessed in a double blind randomized placebo controlled trials in patients with both blunt and penetrating trauma[44-46]. No difference in clinical outcomes and mortality was detected, yet there was a reduction in blood loss and the number of patients requiring transfusion of RBCs and massive transfusion. There is also arterial and venous thrombotic risk associated with use of rFVIIa in trauma patients, as well as other populations[47;48]. Based on these trial results and a Cochrane review of 29 studies[49], rFVIIa is not routinely recommended in resuscitation of trauma patients and its inclusion in massive transfusion protocols is at physician discretion.

As noted previously, TXA was recently shown to reduce 30 day all-cause mortality rates in bleeding trauma patients who received the drug within 3 hours of injury and in particular, within 1 hour from injury, compared to placebo with a relative risk reduction of approximately 10%. The reduction in deaths from bleeding was approximately 15% in

those receiving TXA compared to placebo and 32% reduction if TXA was given within 1 hour [3;11]. Findings were similar in military trauma populations[50]. There were no excess thrombotic complications associated with its use, unlike FVIIa. Additional analyses evaluating cost-effectiveness of TXA in the Crash-2 trial showed that early administration of TXA is likely to be highly cost effective in low, middle, and high income settings[51]. Given the impressive reduction in trauma related death and its cost-effectiveness TXA has been incorporated into trauma treatment guidelines worldwide[52]. Whether the benefit of TXA exists in developed countries is unclear. Most participating countries in Crash-2 were low and middle-income where blood products to treat coagulopathy may not be available, unlike in higher-income countries where MTPs exist in many trauma centres.

Delayed Major Bleeding In Critically Ill Trauma Patients

A review of the literature on delayed major bleeding in critically ill adult trauma patients did not reveal any relevant studies or definitions. There are prediction scores for evaluation of bleeding and risk of hemorrhagic shock after trauma, but their usefulness is uncertain. Civilian data sets have been used to derive nine prediction scores for the need for transfusion, including massive transfusion, following trauma[5-7;53-60]. These scores have been used to guide early and aggressive implementation of blood products[61] and may be used to activate massive transfusion protocols. The scoring systems developed include combinations of factors identified on initial evaluation of bleeding trauma patients such as physiologic, hemodynamic, laboratory, injury severity,

and demographic information[61]. Several of the scores use combinations of dichotomous variables that can be obtained quickly upon assessment of trauma patients presenting to the emergency department. Variables that have been used include the systolic blood pressure, heart rate, hemoglobin levels, pH, lactate levels, base excess/deficit, severity of injury and imaging findings. Examples of these scores are the Shock Index (heart rate divided by systolic blood pressure) which was found to be too insensitive to rule out disease[62] and the TASH score (Trauma Associated Severe Hemorrhage) which uses seven parameters to determine the probability for massive transfusion[63]. The TASH score was retrospectively analysed and validated in the German Trauma registry but it has not yet been widely adopted. The major limitation to these prediction scores is their retrospective design from primarily single centres, with the exception of the Emergency Transfusion Score (ETS) which has been prospectively validated[7;57]. Since no definition for, or risk factors associated with, delayed major bleeding in critically ill adult trauma patients was identified, this emphasized existence of an important knowledge gap. We derived our own definition of delayed major bleeding which was major bleeding that occurs more than 24 hours after presentation to the emergency department. The timeframe of > 24 hours was chosen because the majority of patients who succumb to trauma related major hemorrhage do so during the first 24 hours after injury. It was felt that if patients survived beyond this time period, hemostasis would have been achieved.

Thrombotic Risk in Trauma

Trauma induced coagulopathy results from tissue injury and hypoperfusion due to massive hemorrhage and shock. In contrast to bleeding during early stages following trauma, there is an opposing concern of thrombotic complications during the later phase of trauma[64]. These two entities are on a continuous spectrum and the transition from coagulopathy to a procoagulant state can occur within hours to days if patients survive[65]. The late prothrombotic stage of trauma is similar to the coagulopathy of severe sepsis that leads to multiorgan failure (MOF)[26] and affects patient prognosis[66]. In addition to microvascular thrombosis that leads to MOF, critically ill trauma patients are at risk of large vessel venous thrombosis, in particular deep vein thrombosis (DVT) of the lower extremities and pulmonary embolism (PE), which are collectively called venous thromboembolism (VTE).

Venous Thromboembolism in Trauma Patients

Prospective cohort studies estimate the incidence of DVT in trauma patients at 15% to 60%, depending on diagnostic modalities used and type of prophylactic measures employed [67-71]. In a Canadian single centre prospective observational study, Geerts et al. found the incidence of proximal DVT in 349 trauma patients with an ISS > 9, and in the absence of prophylaxis, was estimated at 18%[69]. Patients were assessed daily for clinical findings of VTE and had appropriate investigations if needed; otherwise, patients underwent routinely scheduled surveillance imaging with contrast venography. The consequence of untreated DVT is a potentially fatal PE and in the absence of

prophylaxis the incidence of PE in major trauma patients is reported to be 0% to 22% which varies with injury severity and other risk factors[67-69;72]. The mortality associated with PE from retrospective database analyses and autopsy studies is 15% to 50%[72-74]. In the study by Geerts et al. the number of patients with confirmed PE was only seven of 39 suspected cases, with three cases confirmed at autopsy[69].

Numerous risk factors for VTE specific to the trauma population have been identified and include: increased age, prolonged immobility due to coma, need for blood transfusion and surgery, high injury severity score, presence of venous injury, delayed initiation of prophylaxis due to bleeding concerns, interruption of anticoagulant prophylaxis, lower extremity or pelvic injuries, spinal cord injuries, and head injuries[67-69;73;75-78].

Although VTE is generally considered a late complication of trauma, it has been seen to occur within the first 24 hours after injury[79-81]. Most centres have subsequently implemented early use of VTE prophylaxis in general trauma patients to minimize the risk of this late and preventable complication.

Venous Thromboembolism Prophylaxis in Critically Ill Patients

Anticoagulant VTE prophylaxis is standard of care for most patients in the intensive care unit including general medical, surgical patients, and trauma patients[82-84]. Exclusions to use of anticoagulants would be in patients perceived to be at high risk of bleeding for various reasons including injury pattern or location. In such settings use of compression devices or stockings is often employed, albeit less effectively than anticoagulants. An

observational study of 294, 896 episodes of critical illness in 271 ICUs in the United States from 2008-2010 showed significantly lower adjusted ICU and hospital mortality rates in patients who received anticoagulant prophylaxis compared to those who received no prophylaxis[85]. Analysis of a large registry of 175, 665 critically ill adults in 134 ICUs in New Zealand and Australia from 2006-2010 showed a significant association between omission of early thromboprophylaxis (anticoagulant and mechanical devices) and hospital mortality after adjusting for covariates, including multiple trauma[86]. A delay in VTE prophylaxis of greater than 24 hours was associated with 66% increased odds of hospital mortality in multi-trauma patients.

In a single centre randomized controlled trial (RCT) of 344 general trauma patients, Geerts et al. demonstrated a significant 58% risk reduction in proximal DVT with use of the low molecular weight heparin (LMWH) enoxaparin 30 mg twice daily compared to unfractionated heparin (UFH) 5000 units twice daily anticoagulant prophylaxis[76]. Anticoagulation was started within 36 hours of injury provided there was no ongoing bleeding. As with the previous study by Geerts et al., this study included patients with ISS > 9 but it excluded patients with frank intracranial bleeding and only 5% had TBI[69;76]. No patients died of PE. Major bleeding complications were infrequent (1.7%) and similar between the two groups (0.6% UFH and 2.9% enoxaparin). A recent systematic review of randomized controlled trials in multi-system trauma patients evaluating bleeding complications of LMWH, compared enoxaparin prophylaxis to other VTE prophylaxis and reported a pooled bleeding risk of 4.7%[87].

Bleeding in Critically Ill Patients

Despite the clear benefit of anticoagulant prophylaxis at reducing rates of proximal DVT, physicians often express concerns of bleeding risk in patients that are in excess of what is actually observed[88-91]. As a result, anticoagulant VTE prophylaxis is delayed and patients are exposed to potential harm of developing fatal PE. Adding to this challenge of balancing bleeding and thrombotic risks is the inability to determine which trauma patient is at risk of delayed major bleeding.

Few studies have examined bleeding complications associated with thromboprophylaxis in trauma, and include specific populations such as those with traumatic brain injury (TBI)[92]. In a prospective study of 525 patients with TBI who were deemed eligible to receive LMWH prophylaxis within 48 h of admission, progressive hemorrhagic changes were seen on head CT scan in 18 patients (3.4%), including in six (1.1%) where a change in management or outcome occurred[93]. To further estimate baseline risk of major bleeding complications, data on patients who received non-anticoagulant prophylaxis in randomized trials of thromboprophylaxis has been reviewed. Only three studies report major bleeding outcomes in four patient groups who did not receive anticoagulant prophylaxis[73;94;95]. The pooled (random-effects) risk of major bleeding was 0.7% (95% CI, 0.2% to 1.7%)[92], and this likely represents the lower limit for baseline bleeding risk as patients considered to be at increased risk of bleeding were excluded from most trials of thromboprophylaxis.

Available literature addressing bleeding complications in critically ill adults is primarily from the general medical-surgical population. A systematic review of critically ill

medical-surgical patients exposed to LMWH thromboprophylaxis reports bleeding complications ranging between 7.2% to 23.1%[96]. This broad range was not specific and encompassed both major and minor bleeding events, which were variably defined by the included studies. The comparative bleeding rate in patients who received placebo in one randomized trial was 15.9%[96]. Similarly, bleeding event rates in critically ill patients with severe renal insufficiency receiving dalteparin prophylaxis were noted at 7.2% for major bleeding[97].

The largest RCT to evaluate bleeding event rates in the general adult critically ill population is the PROTECT study[82]. Nearly 3800 patients were randomized to receive dalteparin or UFH prophylaxis. There was no statistically significant difference in the primary outcome of proximal DVT rates: 5.1% vs. 5.8%, respectively. Major bleeding rates were also similar between groups, 5.5% and 5.6%, respectively. The most common sites of bleeding were: GI tract (52%), surgical site (30%), respiratory tract (16%), retroperitoneal (8%), and intracranial hemorrhage (3.4%)[98]. Independent risk factors for bleeding included hematologic abnormalities of thrombocytopenia and prolonged PTT; use of therapeutic heparin anticoagulation and antiplatelet agents; renal replacement therapy; and lastly, surgery within the preceding three days. The use of either dalteparin or UFH prophylaxis was not associated with increased bleeding events. Patients with major bleeding also had a higher risk of dying in hospital[98].

Tools to Evaluate Bleeding in Critically Ill Adults

Several scores have been developed to predict major hemorrhage and need for massive transfusion immediately following trauma but they have not been widely incorporated into trauma management to measure bleeding in critically ill trauma patients. A prospectively validated tool capturing bleeding events of all severity in 100 general medical-surgical critically ill patients has been developed[99] (Appendix 1). In this single centre study, 20/100 patients experienced 25 major bleeding events (5.2%) and gastrointestinal bleedings were the site of 52% of these bleeds. In this study, the independent risk factors for major bleeding were prolonged PTT and thrombocytopenia. Renal failure and antiplatelet agent use were not associated with increased risk of bleeding. There were also no differences in mortality; however, patients with major bleeding received more blood product transfusion and had longer ICU stay. This tool developed a standardized definition for bleeding severity in the ICU population and there was independent adjudication of bleeding assessments.

In summary, trauma patients are at increased risk of bleeding due to the development of trauma induced coagulopathy which develops within minutes to hours of injury. Comprehensive studies targeting damage control resuscitation have targeted coagulopathy prevention and management, yet the risk of delayed bleeding in critically ill trauma patients who survive the first 24 hours has not been effectively evaluated in the literature. With complex injury patterns and other clinical parameters impacting bleeding risk, one needs to anticipate an even greater potential for delayed major

bleeding in critically ill trauma patients compared to the 5% to 7% event rate observed in the general population of critically ill patients. The evidence to evaluate this bleeding risk in trauma patients is incomplete and identification of risk factors may modify their clinical management.

Objectives of the Thesis

The main objective of the thesis is to answer the research question:

- What is the incidence of delayed major bleeding and what factors are associated with delayed major bleeding in critically ill adult trauma patients who have survived the initial 24 hours of hospitalization?

The overall aim for the research program is to develop a clinical prediction rule for delayed major bleeding in critically ill trauma patients. For the thesis, the first portion of this was initiated by identifying a derivation cohort using adult trauma patients admitted to the Ottawa Hospital Civic campus intensive care unit. The focus was on retrospective review and primary data collection to identify patients with delayed major bleeding, followed by examining baseline characteristics, clinical, laboratory, and procedural variables for importance and to determine which are independently associated with delayed major bleeding in critically ill trauma patients. The second part of the research program will require completion of the derivation cohort and prospective retesting of these independent variables and will be done after completion of the thesis.

Primary Objective:

1) To determine the incidence of delayed major bleeding, defined as bleeding that occurs more than 24 hours after presentation to the emergency department, in critically ill adult trauma patients admitted to The Ottawa Hospital Civic ICU and
2) To describe clinical and laboratory variables associated with delayed major bleeding

Secondary Objective:

To determine the incidence of delayed major bleeding in sub-groups of critically ill adult trauma patients including patients with traumatic brain injury (TBI), splenic and hepatic injuries, those who received massive transfusion within first 24 hours of presentation to the emergency department, and those who received antiplatelet agents at baseline, prior to injury.

Methods

Study Design

A retrospective cohort study was designed and conducted to determine the incidence of delayed major bleeding in critically ill adult trauma patients and characteristics associated with delayed bleeding.

Prior to data analysis there was a change in the definition of delayed major bleeding in the Thesis from that outlined in the Thesis proposal. The time period of bleeding after presentation to the emergency department was shortened from 48 hours (as in the Thesis proposal) to 24 hours for primary objective of the thesis. This change was made because the majority of patients who succumb to trauma related major hemorrhage do so during the first 24 hours after injury. In patients who survived beyond this time period, hemostasis would have been achieved.

Study Setting

The study was conducted at the Ottawa Hospital, Civic Campus intensive care unit. The Civic campus ICU is a thirty-three bed unit with approximately 1200 admissions annually. The Civic campus is the level I trauma centre for the Ottawa region. Approximately 400 patients with Injury Severity Score (ISS) > 15 are admitted per year to the Ottawa Hospital, and approximately half are admitted to the ICU.

Study Period

The time period of the retrospective chart review was initially planned from January 2007 to December 2011. This time period was chosen based on a preliminary assessment of the trauma registry indicating that approximately 1000 trauma patients, with any ISS, required ICU admission. This timeframe was felt to be adequate to evaluate delayed major bleeding rates in critically ill adult trauma patients and to collect patient characteristics potentially associated with increased risk of delayed major bleeding.

This period was subsequently amended to January 2009 to December 2011 because access to charts prior to this was not possible. Electronic medical records became available at the Ottawa Hospital in 2009 and all charts prior to this remain in paper copy and are stored off site.

The thesis proposal was accepted in December 2012. REB approval of the project was granted in February 2013 and access to the Trauma database was provided in March 2013. Data extraction and chart review began in April 2013 and continued until March 2014. Data analyses began in April 2014 and were completed by June 2015.

Study Population

The study population consisted of critically ill adult trauma patients admitted to the Ottawa Hospital, Civic Campus. These patients were identified using the Ottawa Hospital Trauma database and confirmed with chart review via vOacis. The Trauma

Database uses standardized definitions for assigning Abbreviated Injury Scale (AIS) score and subsequent calculation of ISS. The database includes patients with any ISS. The trained data collectors are former Ottawa Hospital Health Records employees who gather patient baseline characteristics, calculate injury severity scores, etc. They make monthly data contributions to the Ontario Trauma Network and are overseen by that organization. Patients identified in the Trauma database were subsequently identified in the electronic medical records system vOacis used at the Ottawa Hospital.

Inclusion Criteria

- Adult trauma patients admitted to the intensive care unit

- Alive after the first 24 hours of admission to hospital

Exclusion Criteria

- Evidence of active bleeding between the first 0-24 hours of hospitalization defined by the requirement for more than 1 red blood cell transfusion in that 24 hour window

    - The exception to this was patients admitted with intracranial bleeding who had evidence of intracranial bleeding on day 2 of admission. This exception was made two reasons: first, because of the critical location of bleeding site; and second, because these patients did not fit our definition for delayed major bleeding. Patients with intracranial hemorrhage often do not have reduction in hemoglobin levels or hemodynamic instability as a result of their major bleeding

events (due to small volume of blood loss). The decision to include patients admitted with ICH and had persistence of ICH on day 2 of admission was made *a posteriori*.

- Patients with known platelet disorder or coagulopathy

- Patients on anticoagulants prior to trauma/injury

Sample Size Calculation

The information provided above with respect to number of ICU admissions annually and the number of trauma patients admitted to hospital annually provided the basis for sample size and time frame of the project.

Proper analyses for association requires 5 – 10 outcomes per predictor variable evaluated in the smallest outcome category[100]. It was anticipated that age, ISS/AIS, mechanism of injury (blunt vs penetrating), vasopressor use, platelet count, PTT, antecedent medications, need for dialysis, and procedures or surgery may be relevant variables, as several of these have been previously identified to be independent predictors of major bleeding in other populations of critically ill adults[92;101]. Therefore a total of 50 to 100 delayed major bleeding events were required to include 10 variables in the final logistic regression model. In patients who experienced more than one bleeding event, only the first event was included in the analysis.

We estimated a risk of delayed major bleeding of 10%. This was a conservative estimate based on recent data from the PROTECT RCT which reported 5.6% major

bleeding rate in general medical and surgical critically ill patients receiving anticoagulant thromboprophylaxis[82]. Similarly, critically ill patients with severe renal insufficiency were found to have a 7.2% major bleeding rate with anticoagulant prophylaxis exposure[97]. It was expected that trauma patients would have an increased risk of delayed bleeding while admitted to ICU, even in the absence of anticoagulant DVT prophylaxis, based on the nature of their injuries and potential for trauma induced coagulopathy.

Based on this risk estimate for delayed major bleeding and the number of outcomes needed per variable in a clinical prediction rule we *a priori* planned to collect data on approximately 800 patients. This would have provided approximately 80 delayed major bleeding events and patients for evaluation in the clinical prediction model. This was a very conservative estimate given that not all variables were expected to be included in the final model.

A total of 66 critically ill adult trauma patients with delayed major bleeding events were captured between September 2010 and December 2011. Given that the number of patients with the required outcome was already obtained and the extensive and complex nature of the data extraction (See section on Data Collection), the total sample size was reduced to 150 patients as per the Thesis Committee recommendations in March 2014.

Subsequent to completion of the thesis the plan is to validate the findings of this work in other databases to confirm generalizability of the predictors and to study the rule prospectively.

Ethics Review

Approval from the Ottawa Hospital Research Ethics Board was obtained for the retrospective audit portion of this project.

Primary Outcome

To describe the incidence of delayed major bleeding occurring in critically ill adult trauma patients at The Ottawa Hospital at least 24 hours after admission to hospital, and defined using the HEME bleeding assessment tool[99]. In patients who experienced more than one bleeding event, only the first event was included in the analysis.

Definition of Delayed Major Bleeding

The HEME bleeding assessment tool[99] was used to identify and define patients with delayed major bleeding (Appendix 1) that occurs at least 24 hours after admission to hospital. This tool has been prospectively validated in a general medical-surgical critically ill population, demonstrating prolonged ICU length of stay and increased number of blood transfusions in patients with major bleeding compared to those with minor or no bleeding. It is the most widely applied tool to identify bleeding events in critically ill patients although it has not previously been used in trauma patients.

Data Collection

Study Variables/Covariates

The following information on each patient was collected from two sources: previously collected injury severity scores from the Ottawa Hospital Trauma database and primary data collection through chart reviews. The data obtained was recorded on an electronic case report form (CRF) created using Microsoft Access software. The CRF maintained patient confidentiality by using a unique study identification number for each patient. The Access database allowed data to be transferred to Microsoft Excel and then to SAS software for analysis. Copies of the CRFs used are available in Appendices 2 and 3.

Data was collected for a maximum of 14 days regardless of duration of ICU admission. This time period was chosen based on the time to major bleeding observed in the PROTECT trial which was a median of 9.5 days (range 6-15.5 days)[98]. The reason for this was that the length of ICU stay in the cohort was as long as one month for some patients and it was felt that bleeding after 14 days was likely to be related to procedures and interventions performed on the patient rather than to the injury itself. This time period fit with the upper limit of the range observed in the PROTECT trial.

Variables from the Ottawa Hospital trauma database:

- Baseline characteristics (collected at hospital admission):
    - Injury severity score (ISS)[102], Abbreviated Injury Scale (AIS)[103] scores, mechanism of injury (fall, motor vehicle collision, etc.), preadmission use of antiplatelets and anticoagulants.

Variables from primary data collection and chart review:

- Baseline Characteristics (collected at hospital admission):
    - Demographics: age and gender of patient
    - Patient comorbidities: renal, lung, cardiac, and liver disease and immunosuppression as defined by the Acute Physiology and Chronic Health Evaluation II (APACHE II) score (Appendix 4); diabetes
    - Medications prior to injury: anticoagulants, antiplatelets (ASA, clopidogrel)
- Organ support values (collected daily during ICU admission):
    - Vitals: heart rate (HR)
    - Vasopressor use
    - Days of mechanical ventilation
    - Need for dialysis
- Laboratory values (collected daily during ICU admission):
    - Hgb, Platelets, PTT, INR, fibrinogen, lactate, pH, creatinine

- Invasive procedures/interventions (collected daily during ICU admission):
    - central line insertion, arterial line insertion, chest tube insertion, surgery (timing of surgery from admission, and duration of surgery)
- Transfusion of blood products (collected daily while in ICU):
    - Number of units/doses of RBCs, FP, platelets, cryoprecipitate, factor VIIa
- Medications administered (collected daily while in ICU):

    - VTE prophylaxis methods: use of UFH, LMWHs, fondaparinux, SCDs, inferior vena cava (IVC) filter insertion, no prophylaxis
    - Therapeutic anticoagulation
    - Antiplatelet agents (ASA, clopidogrel)
    - TXA
- Dates of admission and discharge from ICU and hospital, date of death

For the primary outcome of delayed major bleeding we gathered data corresponding to each criterion of the HEME Bleeding Assessment Tool. Daily hemoglobin levels and administration of transfused RBCs were recorded using The Ottawa Hospital's electronic medical record system, vOacis. Daily nursing notes were reviewed for trends in vital signs including changes in heart rate and systolic blood pressure. These notes were also used to identify overt bleeding in patients and procedures or interventions performed for wound related bleeding. Bleeding and procedures performed were confirmed by reviewing the integrated progress notes of the medical chart, diagnostic imaging reports, and operative notes. Bleeding in critical sites including intracranial bleeding, retroperitoneal bleeding and intra-articular bleeding, was identified from diagnostic imaging reports and operative reports. These variables identifying delayed major bleeding were collected daily. A detailed instruction manual on procedures for data extraction is available in Appendix 5.

Statistical Analysis

Descriptive Statistics

The patient cohort was described according to those with and without delayed major bleeding (present or absent). Continuous independent variables were summarized using means ± standard deviations or medians and ranges as appropriate; categorical variables were described according to numbers and proportions.

The covariates age, ISS, INR, PTT, hemoglobin, platelets, lactate, fibrinogen, and creatinine were treated as continuous variables. All remaining covariates were treated as categorical variables.

The time-dependent variables used in our analysis were the following: lab values (Hgb, platelets, INR, PTT, creatinine), organ support (mechanical ventilation, vasopressor use, use of dialysis), procedures and surgical interventions (tracheostomy, central line insertion, chest tubes), and use of some medications (anticoagulants and antiplatelets).

Univariate Analysis

Univariate analysis was performed to evaluate the strength of association of each variable with the outcome of delayed major bleeding. Univariate analysis of categorical, continuous, and time-dependent variables was examined using Cox proportional hazard modelling. All variables of the univariate analysis were included in multivariate analysis regardless of significance.

Multivariate Analysis

Multivariate analysis for all variables, including time-dependent variables, was evaluated using Cox proportional hazard modelling. Inclusion of all variables in a Cox model is a more rigorous analytical approach than multiple logistic regressions, given the number of time-dependent variables that were included. This analysis was based on that used for evaluation of independent variables associated with major bleeding in the PROTECT trial[98]. Backwards elimination variable selection was performed and variables with $p<0.2$ were kept in the final model.

For the time dependent variables such as coagulation profiles, the most abnormal value within the preceding 72 hours was used in the Cox proportional hazard analysis (i.e. lowest platelet count or highest INR); for organ support measures such as mechanical ventilation, and surgical procedures such as tracheostomy, the presence or absence during the previous 72 hours was used; and for antiplatelet medication (i.e. ASA and clopidogrel), use within the preceding seven days was included. This method was used for patients who experienced a delayed major bleeding event as well as those who did not. The regression model evaluates patients with a delayed major bleeding event compared to those who did not and looks at covariates in each group. This is done daily for up to 14 days of ICU admission, comparing those with and without delayed major bleeding events.

Subgroups

The following subgroups were evaluated for incidence of delayed major bleeding: TBI, splenic and hepatic injuries, those who received massive transfusion, and those who received antiplatelet agents at baseline, prior to injury.

- TBI was categorized as mild (Glasgow Coma Scale (GCS) score 13 – 15), moderate (GCS 9 – 12), and severe (GCS ≤ 8)[104]. CT imaging reports were used to identify new bleeds or increase in size of existing bleeds.
    - Due to the small number of patients with mild TBI, we determined the incidence of delayed major bleeding in the cohort of patients with any severity of TBI.
- Splenic and hepatic injuries were categorized according to the American Association for the Surgery of Trauma grading scales[105]. Grading of injuries to these organs was based on abdominal computed tomography imaging reports. The injury grading scale for the spleen has five levels and that for the liver has six levels. Patients with splenic and hepatic injuries were evaluated for delayed bleeding, regardless of initial management (conservative or surgical).
- Massive transfusion is defined as ≥ 10 units of pRBCs during the first 24 hours from hospital presentation[32;55].
- Antiplatelet medications included antecedent use of ASA and clopidogrel.

The number of patients in this cohort with splenic or hepatic injuries, who received massive transfusion, or were on antecedent antiplatelet agents, was small. The

incidence of delayed major bleeding was determined for these subgroups; however, multivariate analyses to determine risk factors for delayed major bleeding were not performed due to the small sample sizes leading to inability to make meaningful conclusions.

Missing Data

Missing baseline data of ≥ 10% for the entire cohort was managed with imputation. Many imputation strategies exist including simple measures such as carrying the last observation forward, to more sophisticated approaches such as multiple imputation procedures and regression methods[106].For this thesis, the imputation methods that were used were: for continuous variables, imputation using the group mean from the existing data; categorical variables used group proportions from existing data with missing values randomly assigned to the categories in the same proportion as the observed proportions. We did not anticipate missing much baseline data. For variables with > 15% of data is missing, we removed the variable from analysis.

Interobserver Reliability

The evaluation of reviewer agreement addressed two important issues. The first was to ensure agreement on whether the delayed major bleeding event occurred, and the second was agreement on the characteristics of all delayed major bleeding events. (1) To address whether a major bleed occurred, a random sample of 10% of patients

identified as having a major bleed and another random sample of 10% of patients that were not identified as having a major bleeding event and who had an ISS score of at least 20 (indicating moderate to severe injury and higher likelihood of a major bleed to have occurred) were combined and examined by a second independent reviewer (JS and/or LC). If there was disagreement, such that the second independent reviewer identified a major bleeding event not captured by the first reviewer, all charts were to be re-screened by the second reviewer. (2) To examine agreement on the characteristics of the major bleeding events that occurred for all patients, a second independent reviewer examined 10% of these patients' charts (JS and/or LC).

Data collected by the second reviewer included baseline data (age, sex, ISS and AIS score, patient comorbidities such as diabetes, chronic lung, cardiac, renal, hepatic and immunosuppression as defined by the APACHE II score), previously known risk factors for bleeding (ex: platelets, INR, PTT, use of antiplatelet agents), and for patients that had major bleeding events, all details that defined the major bleed according to the HEME bleeding assessment tool.

A two rater unweighted Kappa statistic was calculated for the interobserver reliability[107]. Kappa is defined as $K = P_0 – P_e/1 - P_e$; where P_0 is the actual probability of agreement and P_e is the expected agreement by chance. A Kappa score > 0.8 is considered excellent reliability, a score > 0.6 is good reliability, and a Kappa score < 0.4 is poor reliability.

Results

The study population included 185 patients obtained from the Ottawa Hospital Trauma database admitted to the Civic Campus ICU between January 2010 and December 2011. One hundred eighty five patients were screened and 35 were excluded; 150 patient charts were used for data extraction. Reasons for patient exclusion are detailed in Figure 1.

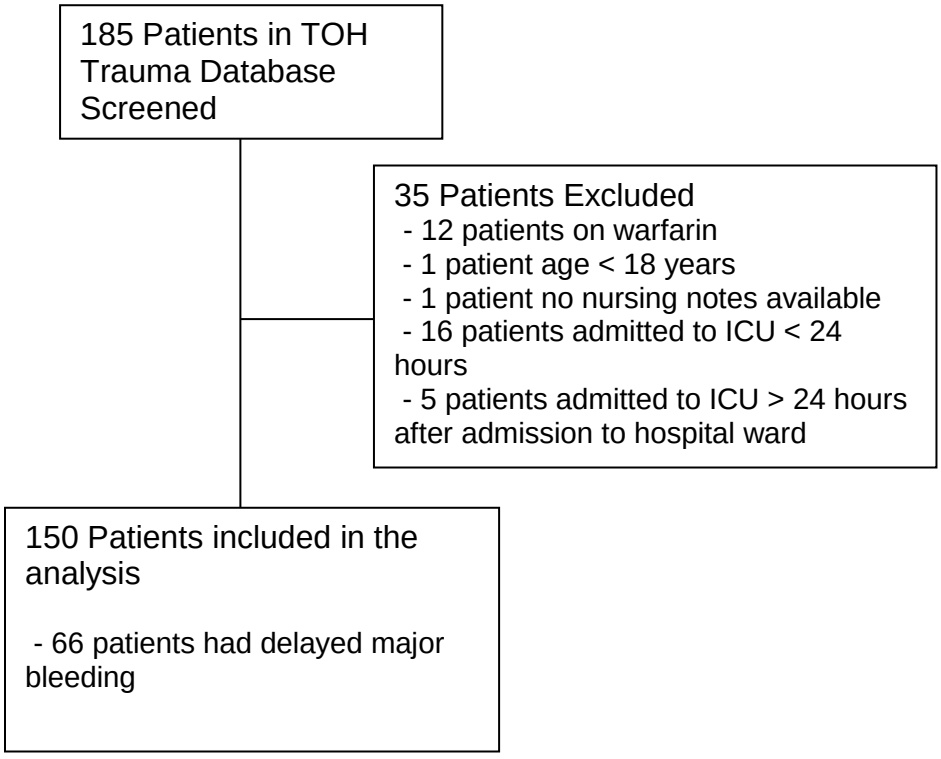

***Figure 1**: Study enrollment and patient exclusions*

Study Patient Characteristics

Delayed Major Bleeding Events

Sixty-six patients (44%) were identified to have delayed major bleeding. The majority of patients with delayed major bleeding had major bleeding at admission to ICU (62/129; 48%) (Table 1). There were 92 criteria meeting the definition for diagnosis of delayed major bleeding in 66 patients; only the first delayed major bleeding events were included in the analyses. The interrater reliability of detecting major bleeding in moderate-severely injured patients using the HEME tool was excellent with a Kappa score of 0.98 (95% CI: 0.96 – 0.99). Reliability of the characteristics of the major bleeding events between two reviewers was slightly lower with a Kappa score of 0.92 (95% CI: 0.89 – 0.95). The most common discrepancies identified were the vital signs (systolic blood pressure and heart rate) changes to describe an overt bleeding event. The reason for challenges in identifying vital sign changes as indicators for delayed major bleeding is that critically ill trauma patients may have had other reasons for fluctuations in heart rate and blood pressure such as septic shock, not only delayed major bleeding.

Baseline characteristics are presented in Table 2 according to the occurrence of delayed major bleeding. Most patients were males who sustained blunt mechanisms of trauma and the majority required mechanical ventilation. TBI was more prevalent in patients with delayed major bleeding (71%) compared to those without delayed major bleeding (49%), as was major bleeding at the time of admission to ICU (94% vs 80%, respectively). Those with delayed major bleeding were more likely to be on antiplatelet

agents prior to injury and to receive blood transfusion and massive transfusion. Details of delayed major bleeding according to severity and anatomical injury site can be found in Appendix 6.

Diagnostic Criteria for Definition of Delayed Major Bleeding

There were 92 diagnostic criteria met for delayed major bleeding using the Heme bleeding assessment tool in 66 patients with delayed major bleeding events. Using this tool to identify delayed major bleeding events, delayed major bleeding was categorized using three broad categories. Proportions reported are for those related to the 92 diagnostic criteria met. The first category was overt bleeding with any one of the following in the absence of other causes: decrease in hemoglobin of 20 g/L or more (25%; 23/92); transfusion of ≥ 2 units RBCs with no increase in hemoglobin (36%; 33/92); decrease in systolic blood pressure by ≥ 10 mmHg (9%; 8/92); and increase in heart rate by ≥ 20 beats per minute (5%; 5/92). The second category for delayed major bleeding was bleeding at any one of the following critical sites: intracranial (39%; 36/92); retroperitoneal (2%; 2/92); intraperitoneal (2%; 2/92); pelvic (4%; 4/92); intra-articular (1%; 1/92); and intra-spinal (epidural) (1%; 1/92). The final category was wound related bleeding requiring intervention (8%; 7/92). Sites of bleeding were not mutually exclusive, such that one patient may have met more than one criterion for delayed major bleeding (e.g. a patient may have had a decrease in hemoglobin of > 20 g/L and had a retroperitoneal bleed).

Sites of Delayed Major Bleeding and Time to Delayed Major Bleeding

The most common sites of delayed major bleeding are shown in Table 3 according to occurrence of major bleeding at admission to ICU. Most episodes of delayed major bleeding occurred in patients with major bleeding at the time of admission and the most common sites of delayed major bleeding included intracranial, respiratory tract, surgical site, and hematuria. The most common sites of major bleeding at admission were intracranial, respiratory tract, and surgical site (Table 4). Patients may have met criteria for major bleeding in multiple anatomical/surgical sites. The median time from ICU admission to first delayed major bleeding was 1 day (range 2-12 days). Seventeen patients admitted with intracranial bleeding had evidence of ongoing intracranial bleeding on day 2 of admission. When these patients were removed from the analysis to determine time to first delayed major bleeding, this was 2 days (range: 2-12 days).

Although there were 17 patients with intracranial bleeding on admission that had persistent or progressive intracranial bleeding on day 2 of admission, these patients were included in the analysis for determinants of delayed major bleeding. The reason for this is based on the location of bleeding in these 17 patients being in a critical site (intracranial) which was felt to be clinically relevant and important to include them.

Subgroups and Delayed Major Bleeding

Subgroups of interest in this cohort included patients with TBI, splenic and hepatic injuries, those who received massive transfusion, and those on antiplatelet medications prior to injury.

Traumatic Brain Injury

A total of 88 patients had TBI and severity according to occurrence of delayed major bleeding is presented in Tables 2 and 5. Seventy-one per cent of patients with TBI had delayed major bleeding. Eighty-five patients had a corresponding GCS available to categorize them according to severity of TBI. Severe TBI was the most common in patients with and without delayed major bleeding, followed by mild and moderate severity. With respect to type of brain injury, all forms were more common in patients with delayed major bleeding with subdural hematoma (SDH) (51.5%), subarachnoid hemorrhage (SAH) (47%), contusion/intracerebral hemorrhage (ICH) (35%), and diffuse axonal injury (DAI) (21%) being the most frequent (Table 5). Patients with multi-compartmental TBI, or bleeding in several regions of the brain (i.e. SAH and SDH), were more likely to have delayed major bleeding (48.5%). Twenty-seven patients (31.8%) admitted with intracranial bleeding were diagnosed with delayed major bleeding that was also intracranial bleeding.

Remaining Subgroups

The number of patients in the cohort with splenic and hepatic injuries was 15 and 20, respectively. Fourteen per cent of patients with splenic injury had delayed major bleeding, as did 17% of patients with hepatic injury. The number of patients who received massive transfusion was 12 and 14% had delayed major bleeding; only 18 patients were on antiplatelet agents prior to injury and 17% had delayed major bleeding (Table 2).

Interventions Received During ICU Admission

Throughout admission to ICU information was captured daily with respect to specific medications or devices used that influence bleeding or thrombotic risk including anticoagulants, antiplatelets, stress ulcer prophylaxis, vasopressors, need for mechanical ventilation, dialysis support and mechanical modes of DVT prevention (Table 6). During ICU admission nearly all patients received stress ulcer prophylaxis and were mechanically ventilated; sequential compression devices (SCDs) were applied to 75% of patients on at least one day of admission. In patients with delayed major bleeding, TXA and vasopressor use were more frequent and these differences were statistically significant compared to those without delayed major bleeding.

Anticoagulant Thromboprophylaxis

Thromboprophylaxis was used in 80% of all patients with LMWH being used more often in patients with delayed major bleeding, although this finding was not statistically significant (Table 6). Patients with delayed major bleeding were more likely than those without delayed major bleeding to have anticoagulant thromboprophylaxis held during ICU admission (Table 6). The most frequently cited reasons for this were current bleeding (86% vs 58%, $p < 0.0002$) and expected surgery or procedure (35% vs 18%, p 0.018).

In patients with delayed major bleeding, 32% (21/66) received anticoagulant thromboprophylaxis (LMWH or UFH) prior to the first delayed major bleeding event. Twenty per cent of patients received LMWH (13/66) and 15% (10/66) received UFH;

some patients may have been given both forms of thromboprophylaxis prior to delayed major bleeding event.

The time to first use of anticoagulant thromboprophylaxis was variable depending on occurrence of delayed major bleeding and presence of major bleeding at time of admission to ICU (Tables 7-9). For the entire cohort of 150 patients the median time to use of any anticoagulant prophylaxis (LMWH or UFH) was 3 days (range 1-13 days); the median time to delayed major bleeding from admission was 2 days (range 2-12 days) (Table 7). In the patients with delayed major bleeding who received any anticoagulant thromboprophylaxis the median time to delayed major bleeding was 3 days (range 2-12 days) and the time to first use was 4 days (range 1-12 days) (Table 8). In the subgroup of patients with delayed major bleeding excluding patients who had intracranial bleeding at admission and intracranial bleeding on day 2 of ICU admission (n=49), the median time to delayed major bleeding was 3 days (range 2-12) and the median time to first use of any anticoagulant prophylaxis was 3.5 days (range 1-13 days) (Table 9).

For patients with major bleeding identified at admission anticoagulant prophylaxis was held for an additional day (3 days) compared to those without bleeding at admission (2 days) (Table 7). In patients who did not experience a delayed major bleeding event (n= 84) the median time to first use of any anticoagulant prophylaxis was 2 days (range 1-12 days); again, for those who experienced major bleeding at admission this was delayed (2.5 days) compared to those who didn't have major bleeding (1 day) (Table 10).

Venous Thromboembolism Diagnosis

There were very few venous thrombotic events in this cohort. Four patients were diagnosed with DVT and one patient had PE. All patients received full therapeutic anticoagulation.

Risk Factors Associated with Delayed Major Bleeding

Univariate Cox Proportional Hazards Regression Analysis

Characteristics evaluated for association with delayed major bleeding included baseline patient characteristics, injury related factors, and time dependent factors including pharmacologic and mechanical interventions, laboratory measurements, and surgeries or procedures. All variables were included in the multivariate analysis.

Laboratory variables where <10% of data was missing were lactate (8.8% missing) and pH (2.3% missing). Fibrinogen levels were missing in > 15% of patients and this variable was not included in the analysis.

Multivariate Cox Proportional Hazards Regression Analysis

The baseline characteristics that were independently associated with risk of delayed major bleeding ($p<0.2$) were male gender and antecedent antiplatelet use. Four injury related factors were significant predictors of delayed major bleeding: ISS, massive transfusion, and two types of intracranial bleeding: extra-axial hemorrhage (a composite

of EDH ± IVH ± SAH ± SDH) and contusion/ICH (Table 11). The only significant time-dependent predictor of delayed major bleeding was pH. No form of anticoagulant thromboprophylaxis was associated with delayed major bleeding.

Clinical Outcomes Related to Delayed Major Bleeding

When compared to patients who did not have delayed major bleeding, patients who had delayed major bleeding had longer mean duration of mechanical ventilation and vasopressor use, longer ICU and hospital length of stay, and received significantly more red blood cell, platelet and frozen plasma transfusions (Table 12). All patients received leukodepleted blood products and platelets were buffy coat derived, not pooled platelet transfusion. The proportions of patients who survived ICU stay and hospitalization was not significantly different.

Clinically Relevant Subgroups and Risk Factors for Delayed Major Bleeding

In patients with delayed major bleeding, we evaluated two subgroups of clinical interest: those without intracranial bleeding on days 1 and 2 of admission and those with TBI.

Patients with delayed major bleeding who had evidence of intracranial bleeding on days 1 and 2 of admission were removed from the cohort (n=17). This was done because it is difficult to determine if intracranial bleeding on day 2 was progression or continuation of bleeding present on day 1 or if it is de novo bleeding. Univariate Cox proportional hazards regression analysis was performed with the same variables evaluated as in the

analysis for the entire cohort. All variables were included in multivariate Cox proportional hazards regression analysis; those variables with $p < 0.20$ remained in the model. The final model is similar to that for the entire cohort; however, antecedent antiplatelet agent use was no longer significant. pH remained significantly associated with delayed major bleeding; and interestingly, the use of antiplatelet agents during ICU admission in this subgroup was also associated with delayed major bleeding (Table 13).

The final subgroup analysed was in patients with traumatic brain injuries ($n = 47$). As with the previous analyses, all variables in the univariate Cox proportional hazards regression analysis were included in the multivariate Cox regression and those variables with $p < 0.2$ remained in the final model. Unlike the model for the entire cohort, gender was not associated with delayed major bleeding, nor was antecedent use of antiplatelet agents or receipt of massive transfusion during the first 24 hours of admission. There were several time dependent variables associated with delayed major bleeding in the subgroup including pH, antiplatelet agent use during ICU admission, and vasopressor use during ICU admission (Table 14).

Discussion

In this retrospective study of critically ill adult trauma patients admitted to The Ottawa Hospital from 2010 to 2011, the incidence of delayed major bleeding was 44%. We also found that male gender, pre-injury use of antiplatelet agents, higher injury severity scores, intracranial bleeding, requirement of massive transfusion, and low pH values were independently associated with delayed major bleeding. Neither type of anticoagulant thromboprophylaxis, LMWH or UFH, predicted delayed major bleeding. The most common sites of delayed major bleeding included intracranial, respiratory tract, surgical bleeding and hematuria. If we remove the patients admitted with intracranial bleeding who had intracranial bleeding on day 2 of admission to ICU (n=17), which may suggest ongoing bleeding rather than new bleeding or recurrent bleeding after hemostasis was achieved, then the delayed major bleeding rate was 33%. It was decided to keep these 17 patients in the cohort even though bleeding on day 2 may have reflected continuous bleeding because the location of bleeding was in a critical site.

The effects of gender on outcomes after trauma have been evaluated in previous studies with divergent results. Some studies report better outcomes for males, while others indicate females do better after severe trauma; others have reported no differences in outcomes based on gender[108]. The outcomes evaluated in these studies include sepsis, inflammatory markers and mortality. Some bleeding models in animals have also reported conflicting results based on gender[109]. Historically, males are more likely to engage in higher risk activities and suffer from penetrating trauma compared to blunt trauma in females[110]. In our trauma cohort the majority of injuries sustained were

blunt trauma and reasons for higher rates of delayed major bleeding in males requires further study.

Use of antiplatelet agents such as ASA and clopidogrel was low which coincides with the relatively young age and comorbid status in this cohort. These agents have irreversible antiplatelet effects lasting up to 7-10 days post-discontinuation contributing to bleeding risk[111]. Use of antiplatelet drugs prior to injury was associated with delayed major bleeding; however, only two patients were taking clopidogrel prior to injury and this association needs further evaluation.

The injury related characteristics associated with delayed major bleeding were intracranial bleeding, higher ISS, and receipt of massive transfusion. The relationship of these variables with bleeding makes sense clinically and is a reflection of degree of injuries sustained.

Acidosis, as measured by blood pH, was also shown to be associated with delayed major bleeding and it is a component of the lethal triad of trauma. Resuscitation efforts in trauma include prevention and reversal of acidosis (see Appendix 7). Treatments for acidosis including sodium bicarbonate and other buffers normalize pH levels but do little to minimize ongoing bleeding in swine models and small human studies that are not powered to detect differences in outcomes[26-28]. A retrospective study of nearly 700 trauma patients compared use of pH levels and base deficits to predict survival[112]. The base deficit was significantly different between those who died and survived, but differences were not seen when the pH was assessed. The role of acidosis, how it is

best measured, and targeted therapies in association with delayed major bleeding require evaluation in larger human studies.

The two subgroups evaluated included patients without intracranial bleeding on days 1 and 2, and those with traumatic brain injury. Risk factors associated with delayed major bleeding in these groups were similar to those for the entire cohort and these associations make sense clinically given the nature and severity of injuries. Use of antiplatelet agents during ICU admission was associated with delayed major bleeding in these subgroups, and this requires further evaluation. Prescription patterns for this seemingly benign medication may change and be limited to those with acute indications such as acute coronary events or ischemic stroke.

The bleeding rates observed in this trauma cohort are much higher than our conservative estimate of 10% which was based on major bleeding rates observed in the PROTECT and DIRECT trials, which reported 5.6% and 7.2%, respectively[82;97]. Both of these trials were multicentre RCTs involving general medical and surgical patients admitted to ICU, and patients received either prophylactic doses of LMWH or UFH for DVT prevention. The DIRECT trial included patients with acute and chronic renal insufficiency. The most common sites of major bleeding in the PROTECT trial were gastrointestinal tract, surgical site, respiratory tract, and retroperitoneum. In that trial six risk factors independently associated with major bleeding were prolonged PTT, low platelet count, use of therapeutic heparin, antiplatelet agents, renal replacement therapy, and surgery[98]. This information was also collected in our cohort of trauma patients, and the only factor associated with delayed major bleeding was antecedent antiplatelet use.

There are several reasons for the discrepancies in variables associated with major bleeding events in the trauma cohort and the PROTECT trial including that the population of critically ill patients are very different, and that the major bleeding events captured in PROTECT were defined differently than that used in this study. Patients in our trauma cohort were younger than those in the PROTECT trial (mean 50 years vs 61years, respectively) and had fewer comorbidities, in particular, renal disease. None of the included patients were dialysis dependent pre-injury and few patients needed dialysis while admitted to ICU; the association between renal failure and bleeding may be related to the associated platelet dysfunction[113], as well as anticoagulation used in the dialysis circuit. Given that few patients were diagnosed with VTE (n = 5) requiring therapeutic anticoagulation, and that we excluded patients who were on warfarin pre-injury, it is not surprising that use of therapeutic heparin was not associated with delayed major bleeding in this cohort.

Prolonged PTT and low platelet counts may not be evident during the early stages post-trauma despite the presence of major bleeding; platelet counts can remain normal but their function may be impaired[64]. These laboratory abnormalities may also be absent in our trauma patients because they received transfusion of blood products in response to major bleeding. The traditional coagulation parameters that were used in our cohort have been criticized as not being appropriate for monitoring and diagnosing trauma associated coagulopathy[114]. Recent studies have suggested using thromboelastography and rotation thromboelastometory for diagnosis of coagulopathy[115;116]; however, these assays are not routinely available and were not available at the time these patients were hospitalized. Whether or not these assays are helpful in predicting delayed major

bleeding has not been evaluated. Although only 14% of patients with delayed major bleeding received massive transfusion, they were significantly more likely to receive platelets (p= 0.02) and frozen plasma (p= 0.0006) compared to patients without delayed major bleeding. Receiving these blood components might have corrected and eliminated any potential association of prolonged PTT and low platelets with delayed major bleeding. It is important to remember that all patients in the PROTECT trial received anticoagulant DVT prophylaxis, possibly altering laboratory levels and subsequent association with increasing bleeding risk.

Surgical procedures was identified as a risk factor for major bleeding in the PROTECT trial but the number of patients who had surgery and experienced major bleeding was <10% of the bleeding cohort and it was associated with a borderline significant p-value of 0.045[98]. All 150 patients in our trauma population had a procedure performed on them, some as minor as arterial catheters and central venous catheters, while others were invasive craniotomies. No procedures individually or collectively were found to be associated with delayed major bleeding.

Approximately 80% of patients received anticoagulant thromboprophylaxis for a least one day during admission to the ICU. Thirty-five per cent of patients received thromboprophylaxis before diagnosis of delayed major bleeding. The median time to first delayed major bleeding was 2 days (range 2-12 days) from admission to ICU and the median time to any anticoagulant thromboprophylaxis in the entire cohort was 3 days (range 1-13) from admission. The overlap in exposure time of these intervals and the lack of an association between DVT thromboprophylaxis and delayed major bleeding is reassuring. This suggests that critically ill trauma patients are likely safe to

receive anticoagulant forms of prophylaxis and that the concerns from clinicians about increased bleeding risk may be unfounded.

The number of patients diagnosed with venous thrombotic events in this trauma cohort is small (3%) compared to previous reports by Geerts et al.[69;76] and in comparison to the general medical and surgical population of the PROTECT trial[82]. The differences for this are related to study methodology as VTE was the primary outcome in these studies and patients had screening imaging (venography or compression ultrasound) performed at defined periods of time during ICU admission to identify presence of DVT. Investigations for PE using CT angiography or ventilation/perfusion scans were performed if there was clinical suspicion of the diagnosis, but routine screening was not done.

Since 2008, the American College of Chest Physicians (ACCP) guidelines have recommended against routine imaging for screening in asymptomatic trauma patients unless they are high risk for VTE (i.e. spinal cord injury or lower extremity injury) and received suboptimal prophylaxis[117]. A similar recommendation was implemented in critically ill patients in the 2012 ACCP guidelines[101]. Whether or not asymptomatic patients diagnosed with VTE in these settings require therapeutic anticoagulation has been debated among clinicians. It is difficult to determine if patients are truly asymptomatic in the ICU when they are frequently intubated or receiving medications that may alter ability to express symptoms. Nonetheless these recommendations have changed practice in critically ill trauma patients leading to lower rates of VTE detection and lower exposure to risks of therapeutic anticoagulation, the most important of which is major bleeding.

Patients who experienced delayed major bleeding required ICU resources for a longer period of time and were mechanically ventilated for longer than patients without delayed major bleeding. The number of additional days of ventilation was 3 days and the average ICU length of stay was 5 days longer for patients with delayed major bleeding. The prolonged admission to a monitored setting would suggest there may be concerns for rebleeding by clinicians. Also included in monitoring for delayed major bleeding is determining the timing of initiating antiplatelet therapy during ICU admission. Whether this monitoring could be done in a monitored step-down unit such at the neuro observation unit or trauma unit at the Civic campus, and what the duration of monitoring should be, is not known and needs future evaluation. Outcomes such as readmission rates to ICU would help delineate resource utilization in this cohort of patients.

There are several strengths and weaknesses of this study. The strengths include derivation of the trauma population from an established trauma database at The Ottawa Hospital. This database is inclusive of all trauma patients presenting to the Ottawa Hospital, and includes patients admitted to the ICU and elsewhere in the hospital. This database is updated monthly by data collectors with prior experience in the Ottawa Hospital Health Records department. They used standardized definitions to determine the AIS and subsequently calculate the ISS. The trained data collectors also collected the patient baseline characteristics, details associated with mechanism of injury (blunt or penetrating), etc. They make monthly data contributions to the Ontario Trauma Network and are overseen by that organization. Given the rigorous structure of the Trauma Database it is unlikely that patients were misclassified in terms of injury severity and mechanism of injury, however, it is possible that some data regarding patient

history and medications is missing given that trauma patients are often unable to provide additional information.

Patients who were on anticoagulation prior to injury were excluded from our patient cohort because we did not want prior use to influence clinician decisions regarding starting of anticoagulant prophylaxis or full therapy while admitted to ICU. If a patient was on warfarin for prior history of DVT or stroke prevention in atrial fibrillation, some clinicians may have started full anticoagulation therapy or prophylaxis earlier which could have exposed patients to increased bleeding risk and higher delayed major bleeding events. Few patients in the screened cohort were on warfarin and this is compatible with the younger age demographic of trauma patients.

Another strength of our study is the agreement between observers in diagnosis of delayed major bleeding and extraction of data. Although the bleeding events were not adjudicated by an independent committee, JS and LC reviewed charts and diagnosed delayed major bleeding prior to data analyses and identification of risk factors associated with delayed major bleeding. We also used a pre-specified bleeding tool and case report forms to collect and record data. The data was extracted from multiple components of the patient chart which corroborated the information obtained. For example, transfused blood products were identified in the blood bank section of the electronic patient chart (vOacis) and confirmed in nursing notes. These measures minimized misclassification bias. In addition, the interrater reliability for diagnosis of delayed major bleeding was excellent with a Kappa score of 0.98.

Limitations of this study include the relatively small sample size, use of a single centre, and those inherent to retrospective cohort studies such as the inability to infer a causal relationship between the identified predictors and delayed major bleeding. The sample size used was much smaller than originally planned making the study underpowered to properly evaluate for predictors of delayed major bleeding and caution should be used when interpreting associations. Although we observed a greater number of events than predicted, this is more likely related to limitations of the definition used for delayed major bleeding. To prove that the observed rate of delayed major bleeding was true would require a much larger sample size. The use of a single centre may introduce bias into the cohort based on specific management practices of trauma patients admitted to the ICU. The indications and thresholds for transfusion or imaging and procedures to be performed may differ between physicians within our own centre as well as other trauma centres. There may also be differences in the patient characteristics compared to other centres making these associations less generalizable to a larger population of critically ill trauma patients. Unmeasurable or unrecorded risk factors related to patient characteristics or trauma itself may have affected the outcome of delayed major bleeding resulting in confounding and an inability to infer causation between the variables associated with delayed major bleeding in our cohort. Other biases introduced by the retrospective design of this study may have resulted in information bias from inconsistent reporting of events/ outcomes and lack of standardized data collection and recording leading to potentially incomplete and unreliable records. This was particularly noted in diagnostic imaging reports where reporting of findings is radiologist dependent

and interpretation of results may lead to a missed delayed major bleeding event, for example.

As noted above, few patients were on antecedent clopidogrel and the association of antiplatelet medications with delayed major bleeding needs to be evaluated in a larger trauma population. The number of patients who received massive transfusion in this cohort was small (n=9) and although a massive transfusion protocol was in place at the time of patient resuscitation in 2010-2011, it is unclear how MTPs were activated and if the use was appropriate. Again, this variable needs to be evaluated more rigorously in a larger cohort and ideally, prospectively to ensure there is adequate power to be confident in these associations.

The HEME bleeding tool used to identify patients with major bleeding was derived in general medical and surgical ICU patients and has not been used in critically ill trauma patients. Although this is a limitation, the components of the bleeding score are in keeping with other definitions of major bleeding [118;119]. No tool for identifying bleeding in trauma patients currently exists and applying any of the existing bleeding tools or definitions would have similar limitations.

The association of acidosis, measured by low pH, with delayed major bleeding has not been reported before in the literature. Physiologically the association to bleeding makes sense as acidosis is known to exacerbate bleeding and its prevention and reversal are included in bleeding management guidelines. pH is a time-dependent variable and its values are influenced by both metabolic and respiratory conditions. Presumably the effects of metabolic changes are the driving force behind this association of pH with

delayed major bleeding given that changes to ventilator settings results in more rapid correction of acid-base abnormalities. Patients with acidosis also likely received sodium bicarbonate for neutralization but we are unable to determine this uniformly as sodium bicarbonate administration may not be recorded during resuscitation efforts in nursing notes. As noted above, base deficits may also be a better measure of acid-base status, and whether or not neutralization of pH modifies the association with delayed major bleeding needs to be evaluated in a larger group of patients.

Other limitations of this study include the coagulation parameters available at The Ottawa Hospital and whether these are the correct assays to use in patients suffering from trauma associated bleeding. Currently we do not have access to newer ROTEM assays which provide information on time to clot formation and clot stability[114]. Studies have also shown that early drop in fibrinogen levels may be a better reflection of trauma induced coagulopathy but there are conflicting reports on this[114]. In our cohort, fibrinogen levels were captured in only 15-20% of patients so this variable was not included in the univariate analysis. Prospective studies should look at comparison of traditional coagulation parameters with newer assays like thromboelastography and regular monitoring of fibrinogen levels for association with bleeding risks.

Lastly, including patients in the cohort who had evidence of intracranial bleeding on days 1 and 2 of admission makes the diagnosis of delayed major bleeding challenging. It is difficult to determine if bleeding on day 2 of admission is progression/extension of bleeding present on day 1 or if it is a new source of bleeding. We included these patients because the location of the bleeding is in a critical site and is clinically relevant. These patients do not fit the criteria used for delayed major bleeding in our study as the

volume of bleeding in the brain is not frequently associated with a drop in hemoglobin of at least 20 g/L, nor is it often associated with hemodynamic instability. Despite these circumstances, the interrater reliability for these patients remained quite high between the data reviewers. An association or interaction between ISS and TBI must also be acknowledged. ISS incorporates the abbreviated injury score for head and neck trauma and overlap with TBI may exist; however, we were not able to assess this.

Conclusions

The delayed major bleeding rate observed in this retrospective review of 150 critically ill trauma patients was 44%. Risk factors associated with these events included male gender, antecedent antiplatelet use, injury severity scores, intracranial bleeding, massive transfusion, and acidosis. While the sample size was smaller than originally planned the event rate was much higher than estimated. Re-evaluating the sample size needed to detect an association between risk factors and occurrence of delayed major bleeding will allow us to continue working to answer this important question. Areas for future work in the trauma population assessment for delayed bleeding risk include continuing with a retrospective review to obtain a larger sample size. This may uncover additional factors associated with bleeding. In addition we will aim to externally validate the variables found to be independently associated with delayed major bleeding in other similar trauma databases, as well as plan for a prospective evaluation in critically ill trauma patients.

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Tables

Table 1: Distribution of Delayed Major Bleeding According to Presence of Major Bleed at Admission

	Major Bleed at Admission (n=129)	No Major Bleed at Admission (n=21)	TOTAL (N=150)
Delayed Major Bleeding, n (%)	62 (48.1 %)	4 (19.1 %)	66 (44.0 %)

Table 2: Baseline Characteristics according to Occurrence of Delayed Major Bleeding

Patient Characteristics	No Delayed Major Bleed (n=84) (%)	Delayed Major Bleed (n=66) (%)
Age (Mean ± SD), years	52. 2 ± 21.5	48.3± 20.1
Male gender	54 (64.3 %)	54 (81.8 %)
ISS (Mean ± SD)	23.7 ± 12.1	33.0 ± 13.9
Mild ≤ 9	7 (8.3 %)	1 (1.5 %)
Moderate 10-24	41 (48.8 %)	14 (21.2 %)
Severe ≥25	36 (42.9 %)	51 (77.3 %)
Mechanism of Injury		
Blunt		
MVC	26 (31.0 %)	32 (48.5 %)
Fall	38 (45.2 %)	26 (39.4 %)
Other	9 (10.7 %)	7 (10.6 %)
Penetrating		
shooting	3 (3.6 %)	1 (1.5 %)
stabbing	7 (8.3 %)	0 (0.0 %)
other	1 (1.2 %)	0 (0.0 %)
Arrived intubated to ER	24 (28.6 %)	9 (13.6 %)
GCS on arrival to ER (highest) (Mean± SD)	9.1 ± 5.5	9.3 ± 4.5
Median (IQR)	10 (3-15)	9 (6-14)
TBI	41 (48.8 %)	47 (71.2 %)
TBI (severity)		
mild	11 (13.1 %)	14 (21.2 %)
Moderate/severe	28 (33.3 %)	32 (48.5 %)
Splenic and/or hepatic injury	14 (16.7 %)	16 (24.2 %)

Patient Characteristics	No Delayed Bleed (n=84)	Delayed Bleed (n=66)
Major bleeding at admission	67 (79.8 %)	62 (93.9 %)
Baseline life support, n		
Mechanical ventilation	74 (88.1 %)	61 (92.4 %)
Vasopressors	35 (41.7 %)	39 (59.1 %)
RBC transfusion (units in first 24h) (Mean± SD)	1.06 ± 2.4	3.39 ± 5.0
Massive transfusion	3 (3.6 %)	9 (13.6 %)
Location before ICU admission		
ER	45 (53.6 %)	39 (59.1 %)
OR/PACU	26 (31.0 %)	18 (27.3 %)
ward	4 (4.8 %)	5 (7.6 %)
Other hospital/ICU	8 (9.5 %)	4 (6.1 %)
Antecedent antiplatelet drugs∫	7 (8.3 %)	11 (16.7%)
Comorbidities at baseline¥	15 (17.9%)	8 (12.1%)
History of GI bleeding	0	0
History of ICH	1 (1.2 %)	1 (1.5 %)

∫ = ASA and/ or clopidogrel

¥ = composite of DM, cardiac, immunosuppression, liver disease, renal disease, respiratory disease (patients may have had more than one illness)

Table 3: Sites of delayed major bleeding events in patients (n = 66) with and without major bleeding at admission

Site of Bleeding	Number of diagnostic criteria for delayed major bleeding (%)	
	With major bleeding at admission (total = 84)	Without major bleeding at admission (total = 8)
Gastrointestinal	6 (7.1)	0 (0)
Surgical site	32 (38.1)	2 (25.0)
Respiratory	33 (39.3)	0 (0)
Retroperitoneal	1 (1.2)	1 (12.5)
Intraperitoneal	2 (2.4)	0 (0)
Intracranial	35 (41.7)	1 (12.5)
Epidural	1 (1.2)	0 (0)
Intra-articular	1 (1.2)	0 (0)
Pelvic	3 (3.6)	1 (12.5)
Device related: external ventricular drain (EVD)	0 (0)	0 (0)
Other		
Wounds/lacerations	8 (9.5)	0 (0)
Epistaxis	2 (2.4)	0 (0)
Hematuria	10 (11.9)	0 (0)
Oral	6 (7.1)	0 (0)
Procedure related	7 (8.3)	4 (50.0)

This table presents the sites of delayed major bleeding in those with major bleeding at admission (62 patients) and those without major bleeding at admission (4 patients). Sites of bleeding are not mutually exclusive.

Table 4: Site of Major Bleeding at Admission according to Occurrence of Delayed Major Bleeding

Site of Bleeding	Number of patients	% of Patients with major bleeding at admission, n = 129	% of overall cohort, n = 150
Gastrointestinal	9	7.0 %	6.0%
Surgical site	33	25.6 %	22.0%
Respiratory	53	41.1 %	35.3 %
Retroperitoneal	12	9.3%	8.0%
Intraperitoneal	18	14.0%	12.0%
Intracranial	85	65.9%	56.7%
Epidural	9	7.0%	6.0%
Intraarticular	2	1.6%	1.3%
Pelvic	5	3.9%	3.3%
Device related: external ventricular drain (EVD)	1	0.8%	0.7%
Other			
Wounds/lacerations	17	13.2%	11.3%
Epistaxis	4	3.1%	2.7%
Hematuria	14	10.9%	9.3%
Oral	6	4.7%	4.0%
Procedure related	10	7.8%	6.7%

This table presents the sites of major bleeding at admission among 129 patients.
Sites of bleeding are not mutually exclusive.

Table 5: Subgroup of TBI

	No Delayed Major Bleed (n=84)	Delayed Major Bleed (n=66)
TBI (present)	41 (48.8 %)	47 (71.2 %)
TBI (severity)		
mild	11 (13.1 %)	14 (21.2 %)
moderate	4 (4.8 %)	9 (13.6 %)
severe	24 (28.6 %)	23 (34.8 %)
Brain Injury (type)		
Extra-axial hemorrhage∫	35 (41.7%)	43 (65.2%)
EDH	4 (4.8 %)	5 (7.6 %)
IVH	6 (7.1 %)	13 (19.7 %)
SAH	27 (32.1 %)	31 (47.0 %)
SDH	25 (29.8 %)	34 (51.5 %)
Contusion/ ICH	25 (29.8 %)	23 (34.9 %)
DAI	8 (9.5 %)	14 (21.2 %)
Multi-compartmental TBI	27 (32.1 %)	32 (48.5 %)

∫ Extra-axial hemorrhage = EDH ± IVH ± SAH ± SDH

Eighty-five patients had GCS available to determine severity of TBI.

Twenty-seven patients admitted with ICH also had delayed intracranial bleeding (31.8%)

Table 6: Pharmacologic or Mechanical Interventions Used During ICU Admission*

Intervention	No Delayed Major Bleeding (n=84)	Delayed Major Bleeding (n=66)	P – value
Medication – no. (%)			
ASA	7 (8.3%)	8 (12.1%)	0.44
Clopidogrel	0 (0.0%)	1 (1.5%)	0.26
Stress ulcer prophylaxis	83 (98.8%)	65 (98.5%)	0.86
Therapeutic LMWH	3 (3.6%)	1 (1.5%)	0.44
Therapeutic IV UFH	3 (3.6%)	2 (3.0%)	0.85
Warfarin	1 (1.2%)	0 (0.0%)	0.37
TXA	2 (2.4%)	8 (12.1%)	0.018
Any VTE Prophylaxis	67 (79.8%)	53 (80.3%)	0.93
Prophylactic LMWH	42 (50.0%)	39 (59.1%)	0.27
Prophylactic UFH	34 (40.5%)	24 (36.4%)	0.61
Reason No Anticoagulant Prophylaxis Used – no. (%)			
At risk of bleeding	41 (48.8%)	37 (56.1%)	0.38
Current bleeding	49 (58.3%)	57 (86.4%)	0.0002
Expected surgery/procedure	15 (17.9%)	23 (34.8%)	0.018
Oversight	11 (13.1%)	13 (19.7%)	0.27
Suspected/ confirmed HIT	0	0	
Mechanical Prophylaxis – no. (%)			
SCDs	59 (70.2%)	53 (80.3%)	0.16
TEDS	55 (65.5%)	43 (65.2%)	0.97
IVC Filter	3 (3.6%)	7 (10.6%)	0.09
Life Support measures – no. (%)			
Mechanical Ventilation	79 (94.0%)	63 (95.5%)	0.70
Vasopressor use	44 (52.4%)	51 (77.3%)	0.0017

* Intervention occurred on at least one day during ICU admission

Table 7: Time to First Use of DVT Prophylaxis in the entire cohort (n=150)

Type of DVT Prophylaxis, n	Time to Use, days; median (range)
Any*, 120	3 (1-13)
Without major bleeding at admission, 21	2 (1-6)
With major bleeding at admission, 99	3 (1-13)
LMWH, 81	3 (1-14)
Without major bleeding at admission, 12	3 (1-13)
With major bleeding at admission, 69	3 (1-14)
UFH, 58	3 (1-12)
Without major bleeding at admission, 13	1 (1-3)
With major bleeding at admission, 45	3 (1-12)

*denotes LMWH or UFH

Table 8: Time to First Use of DVT Prophylaxis in Patients with Delayed Major Bleeding (n=66)

Type of DVT Prophylaxis, n	Time to Event, days; median (range)	
	Delayed Major Bleed	Prophylaxis
Overall cohort, 66	2 (2-12)	--
Any*, 53	3 (2-12)	4 (1-13)
Without major bleeding at admission, 4	2.5 (2-9)	2 (2-3)
With major bleeding at admission, 49	3 (2-12)	4 (1-13)
LMWH, 39	3 (2-12)	4 (1-13)
Without major bleeding at admission, 3	3 (2-9)	2 (2-3)
With major bleeding at admission, 36	3 (2-12)	5 (1-13)
UFH, 24	3 (2-10)	4 (1-12)
Without major bleeding at admission, 1	2 (-)	2 (-)
With major bleeding at admission, 23	3 (2-10)	4 (1-12)

*denotes LMWH or UFH

Table 9: Time to First Use of DVT Prophylaxis in Subgroup of Patients with Delayed Major Bleeding (excluding patients with ICH at admission who had ICH on day 2 of ICU admission) (n=49)

Type of DVT Prophylaxis, n	Time to Event, days; median (range)	
	Delayed Major Bleed	Prophylaxis
Overall cohort, 49	3 (2-12)	--
Any*, 42	3 (2-12)	3.5 (1-13)
LMWH, 31	3 (2-12)	4 (1-13)
UFH, 18	3 (2-10)	4.5 (1-12)

*denotes LMWH or UFH

Table 10: Time to First Use of DVT Prophylaxis in Patient without Delayed Major Bleeding (n=84)

Type of DVT Prophylaxis, n	Time to Use, days; median (range)
Any*, 67	2 (1-12)
Without major bleeding at admission, 17	1 (1-6)
With major bleeding at admission, 50	2.5 (1-12)
LMWH, 42	3 (1-14)
Without major bleeding at admission, 9	3 (1-13)
With major bleeding at admission, 33	3 (1-14)
UFH, 34	2 (1-12)
Without major bleeding at admission, 12	1 (1-3)
With major bleeding at admission, 22	3 (1-12)

*denotes LMWH or UFH

Table 11: Risk Factors for Delayed Major Bleeding: Multivariate Cox Proportional Hazards Analysis

	Hazard Ratio (95% CI)	P – value
Baseline and Injury Related Factors		
Gender (F:M)	0.45 (0.24 – 0.87)	0.017
Antecedent antiplatelet drugs¥	2.11 (1.07 – 4.18)	0.031
ISS (5 point increase)	1.12 (1.03 – 1.22)	0.007
Type of Intracranial bleeding		
Extra-axial hemorrhage∫	3.05 (1.70 – 5.47)	0.0002
Contusion/ICH	0.67 (0.38 – 1.18)	0.167
Massive Transfusion	2.53 (1.05 – 6.08)	0.038
Time dependent Factors		
pH (0.1 unit decrease)	1.41 (1.08 – 1.84)	0.013

This table presents risk factors for delayed major bleeding, using multivariable time-to-event Cox regression analysis. Time-dependent risk factors were considered in the preceding 3 days. Covariates included in the model were those with p-values <0.2 following backwards elimination.
¥ = ASA and/ or clopidogrel
∫ = EDH ± IVH ± SAH ± SDH

Table 12: Blood products transfused*, duration of mechanical ventilation and vasopressors, ICU and hospital length of stay, and discharge status

	No Delayed Major Bleed (n=84)	Delayed Major Bleed (n=66)	P – value
Units PRBCs transfused^, mean ± SD	1.2 ± 2.5, n = 27	4.9 ± 6.4, n = 45	<0.0001
Doses of platelets transfused^, mean ± SD	0.1 ± 0.5, n = 8	0.4 ± 0.8, n = 15	0.02
Units of FP transfused^, mean ± SD	0.6 ± 1.9, n = 9	2.6 ± 4.7, n = 23	0.0006
Units of cryoprecipitate transfused^, mean ± SD	0.3 ± 1.5, n = 3	0.6 ± 2.8, n = 9	0.3
Duration of mechanical ventilation (days), mean ± SD	5.3 ± 4.2	8.4 ± 4.7	<0.0001
Duration of vasopressors (days), mean ± SD	2.2 ± 3.3	3.2 ± 2.8	0.046
Duration of ICU stay (days)			
Mean ± SD	9.9 ± 10.4	15.2 ± 12.4	0.005
Median (IQR)	7 (4-12)	12 (7-21)	0.0002
Duration of hospital stay (days)			
Mean ± SD	28.6 ± 36.0	49.2 ± 72.3	0.02
Median (IQR)	14 (9-31)	28 (11-51)	0.02
Alive at ICU Discharge	71 (84.5 %)	49 (74.2 %)	0.12
Alive at Hospital Discharge	68 (81.0 %)	46 (69.7 %)	0.11

*sum over the entire ICU admission (total FP transfused, total days of MV, etc.)
^ Per patient who had transfusions

Table 13: Risk Factors for Delayed Major Bleeding excluding patients with ICH on days 1 and 2 (n=49): Multivariate Cox Proportional Hazards Analysis

	Hazard Ratio (95% CI)	P – value
Baseline and Injury Related Factors		
Gender (F:M)	0.47 (0.23 – 0.97)	0.040
ISS (5 point increase)	1.14 (1.04 – 1.25)	0.006
Type of Intracranial bleeding		
Extra-axial hemorrhage[∫]	1.84 (0.999 – 3.38)	0.051
Massive Transfusion	3.99 (1.58 – 10.08)	0.004
Time dependent Factors		
pH (0.1 unit decrease)	1.35 (1.004 – 1.81)	0.047
Antiplatelet agent use during ICU admission[¥]	2.99 (1.11 – 8.07)	0.03

This table present the independent risk factor for delayed major bleeding, using multivariable time-to-event Cox regression analysis. Time-dependent risk factors were considered in the preceding 3 days. Covariates included in the model were those with p-values <0.2 following backwards elimination.

∫ = EDH ± IVH ± SAH ± SDH

¥ = ASA use

Table 14: Risk Factors for Delayed Major Bleeding in patients with TBI (n=47): Multivariate Cox Proportional Hazards Analysis

	Hazard Ratio (95% CI)	P – value
Baseline and Injury Related Factors		
Age	0.99 (0.97 – 1.01)	0.175
Antecedent antiplatelet drugs[¥]	2.55 (1.04 – 6.33)	0.041
ISS (5 point increase)	1.12 (0.99 – 1.26)	0.071
Type of Intracranial bleeding		
Extra-axial hemorrhage[∫]	3.38 (1.13 – 10.10)	0.029
Contusion/ICH	0.47 (0.25 – 0.90)	0.023
Time dependent Factors		
pH (0.1 unit decrease)	1.82 (1.19 – 2.79)	0.006
Antiplatelet agent use during ICU admission[§]	2.71 (0.83 – 8.87)	0.099
Vasopressor use during ICU admission	2.01 (1.03 – 3.95)	0.042
Lowest platelet count	1.002 (1.000 – 1.004)	0.027

This table present the independent risk factor for delayed major bleeding, using multivariable time-to-event Cox regression analysis. Time-dependent risk factors were considered in the preceding 3 days. Covariates included in the model were those with p-values <0.2 following backwards elimination.

¥ = ASA and/ or clopidogrel

∫ = EDH ± IVH ± SAH ± SDH

§ = ASA use

Appendices

Appendix 1: HEME Bleeding Assessment Tool[99]

Bleeding Severity

Fatal Bleeding description: _____

Major Bleeding (Bleeding meeting any criterion below)

1. Overt bleeding with ANY ONE of the following in the absence of other causes:
    - Decrease in hemoglobin of 20g/L or more
    - Transfusion of 2 or more units of RBCs with no increase in Hg
    - Decrease in systolic BP by 10mmHg or more while patient sitting up
    - Spontaneous decrease in systolic BP of 20mmHg or more
    - Increase in heart rate by 20 bpm or more
2. Bleeding at ANY ONE of the following critical sites:
    - Intracranial
    - Intraspinal
    - Intraocular (not subconjunctival)
    - Pericardial
    - Retroperitoneal
    -Intraarticular (non-traumatic)
3. Wound related bleeding requiring an intervention:

    Specify intervention:_____

Minor Bleeding: bleeding that did not meet criteria for fatal or major bleeding

Appendix 2: Case Report Form for Baseline Demographics and Patient Status

Bleeding in Trauma Patient Status Form: **Patient ID:** ☐☐☐

1. **Age at ICU admission:** ☐☐☐ **3. Hospital admit date:** (mm/dd/yyyy) ☐☐ ☐☐ ☐☐☐☐

2. **Gender:** ☐ Male ☐ Female **4. ICU admit date:** (mm/dd/yyyy) ☐☐ ☐☐ ☐☐☐☐

5. **Injury severity score (ISS):** ____#____: mild ISS ≤ 9 ☐ moderate ISS 10-24 ☐ severe ISS ≥ 25 ☐

6. **Max Abbreviated injury scale:** 1☐ 2☐ 3☐ 4☐ 5☐ 6☐

Body region:		AIS score:	
1 = head	4 = abdomen	1 = minor	4 = severe
2 = neck	5 = extremity/pelvic	2 = moderate	5 = critical
3 = chest	6 = external/burn	3 = serious	6 = unsurvivable

7. **Mechanism of injury: a) Blunt** ☐ MVC ☐ Fall ☐ Other ☐ _____ **b) Burn** ☐
c) Penetrating ☐ Stabbing ☐ Shooting ☐ Other ☐ _____

8. **Location immediately prior to ICU:** ER ☐ OR/PACU ☐ ward ☐ other hospital/ICU ☐

9. **Brain injury** (check all that apply)**:** SDH ☐ SAH ☐ IVH ☐ EDH ☐ contusion/ICH ☐ DAI ☐ edema ☐ other _____

10. **GCS (arrival in ER):** ____#____; intubated ☐ **11. TBI:** mild (GCS 13-15) ☐ moderate (GCS 9-12) ☐ severe (GCS ≤8) ☐

12. **Splenic injury:** Yes ☐ No ☐ **13. Hepatic injury:** Yes ☐ No ☐

14. **PRBC transfusion** (# units during 1st 24h)**:** _____ **15. Massive transfusion** (≥ 10 units during 1st 24h)**:** yes ☐ no ☐

16. **Antiplatelets** (prior to injury): ASA ☐ clopidogrel ☐ other ☐ _____

17. **Comorbidities** (prior to injury, as per APACHE II score)**:**
a) renal disease: on dialysis: yes ☐ no ☐
b) liver disease: cirrhosis/ portal HTN (± GIB)/encephalopathy: yes ☐ no ☐
c) cardiac: NYHA class IV: yes ☐ no ☐
d) respiratory: documented hypoxia/hypercapnia/ pulm HTN (>40mmHg)/ ventilator dependence: yes ☐ no ☐
e) immunocompromised: chemo/XRT/high-dose steroids/leukemia/lymphoma/AIDS: yes ☐ no ☐
f) diabetes: yes ☐ no ☐
g) bleeding history (in previous 3 mos) : i) GI bleed: yes ☐ no ☐ ii) intracranial bleed: yes ☐ no ☐
iii) other (hematuria, etc) ☐ _____

18. **ICU discharge:** ☐ Alive ☐ Dead ☐☐ ☐☐ ☐☐☐☐ (mm/dd/yyyy)

19. **Hospital discharge:** ☐ Alive ☐ Dead ☐☐ ☐☐ ☐☐☐☐ (mm/dd/yyyy)

Appendix 3: Case Report Form for Data Collected Daily

Bleeding in Trauma Daily Data Form: **Patient ID:** ☐☐☐

Date of Study Day: ☐☐ ☐☐ 2 0 ☐☐ (mm/dd/yyyy) **Study Day:** ☐☐☐

1. **Pharmacologic interventions in past 24 hours** (Check all that apply):
   - ☐ 1. Prophylactic LMWH: (Drug and dose) _____ ☐☐☐☐ ; frequency – daily ☐ BID ☐
   - ☐ 2. Prophylactic UFH: (Dose) ☐☐☐☐ IU; frequency – daily☐ BID ☐ TID ☐
   - ☐ 3. Prophylactic Fondaparinux: (Dose) ☐☐.☐
   - ☐ 4. No Prophylactic anticoagulation given (check all that apply):
     - ☐ 1=Procedure or surgery
     - ☐ 2=Bleeding
     - ☐ 3=High bleeding risk
     - ☐ 4=HIT or suspected HIT
     - ☐ 5=possible oversight
     - ☐ 6=other _____
   - ☐ 5. Therapeutic UFH (infusion, use with CRRT)
   - ☐ 6. Therapeutic LMWH: (Drug and dose) _____ ☐☐☐☐☐ ; frequency – daily ☐ BID ☐
   - ☐ 7. Therapeutic anticoagulation given, reason: _____
   - ☐ 8. Warfarin
   - ☐ 9. ASA
   - ☐ 10. Clopidogrel
   - ☐ 11. Tranexamic acid: (Dose)_____
   - ☐ 12. Stress ulcer prophylaxis (ranitidine, lansoprazole, pantoprozole, etc.)
   - ☐ 13. Other: Argatroban, tPA, TNK (specify drug and dose): _____

2. **Other Interventions in past 24 hours** (Check all that apply):
   - ☐ 1. Mechanical ventilation: invasive ☐ non-invasive ☐
   - ☐ 2. Vasopressor or inotrope infusion
   - ☐ 3. Dialysis ☐ IHD ☐ CRRT ☐ other (specify): _____
   - ☐ 4. Surgery or procedure (e.g. central line, trach), specify: _____
     - Duration of surgery: _____hours; # days from admission to OR: _____day(s)
   - ☐ 5. Antiembolic stockings ☐ 6. SCDs ☐ 7. IVC Filter

3. **Lab Results in past 24 hours:**

   Hgb (g/L) ☐☐☐ (lowest) Platelets (x10^9/L) ☐☐☐ (lowest) INR ☐☐.☐ (highest) PTT (s) ☐☐☐ (highest) Cr (μmol/L) ☐☐☐ (highest)

   Fibrinogen (g/L) ☐.☐ (lowest) Lactate (mmol/L) ☐.☐ (highest) pH ☐.☐☐ (lowest)

4. **Transfusion of Blood Products in past 24 hours:**
   - ☐ PRBCs: _____unit(s) ☐ FFP: _____unit(s) ☐ Platelets: _____dose(s) ☐ Octaplex: _____unit(s)
   - ☐ Cryoprecipitate: _____unit(s) ☐ Factor VIIa: _____unit(s)

5. **Bleeding site** (check all that apply):
   - ☐ 1. GI: ☐ NG blood ☐ hematemesis ☐ melena ☐ hematochezia/BRBPR ☐ UGIB on endoscopy
   - ☐ 2. Respiratory: ☐ hemoptysis ☐ ETT/tracheostomy aspirate ☐ Chest tube ☐ hemothorax
   - ☐ 3. Surgical site: ☐ incision ☐ drain ☐ line insertion site
   - ☐ 4. Retroperitoneal ☐ 5. Intraperitoneal ☐ 6. Intracranial ☐ 7. Epidural/perispinal ☐ 8. Intra-articular
   - ☐ 9. Pelvic ☐ 10. Devices (ICP monitor, etc.)_____
   - ☐11. Other (e.g. intraocular, pericardial): _____

6. **Major Bleeding,** defined as one of the following: (check all that apply)
   - ☐ 1. Life threatening bleed due to hypovolemic shock: ☐ UGIB ☐ LGIB
     - ☐ other, specify: _____
   - ☐ 2. Life threatening bleed into critical site: ☐ intracranial ☐ pericardial ☐ retroperitoneal
     - ☐ other, specify: _____
   - ☐ 3. Bleeding that requires invasive intervention, specify procedure: _____
   - ☐ 4. Clinically important bleeding: Overt bleeding and one of the following within 24h and absence of other causes
     - ☐ drop in Hgb ≥ 20 g/L ☐ transfused ≥ 2 units ☐ other, specify: _____
     - ☐ drop in SBP of ≥ 20mmHg ☐ increase in HR by ≥ 20 bpm

7. **Major Bleeding event:** no ☐ yes ☐ **8. Minor bleed,** bleeding that did not meet major bleeding criteria: ☐
9. **Timing: New bleed** ☐ **Recurrent bleed** (same site) ☐ **Duration of bleeding: _____hrs**
10. **Time to 1st major bleed** (from admission to ICU): **_____hrs**
11. **Was the patient discharged from ICU today?** ☐ no ☐ yes, complete Patient Status form

Appendix 4: Acute Physiology and Chronic Health Evaluation II Score (APACHE II)

Definition of chronic diseases includes:

Organ insufficiency or immune-compromised state must have been evident prior to this hospital admission and conform to the following criteria:

Liver: biopsy proven cirrhosis and documented portal hypertension; past upper GI bleeding attributed to portal hypertension; prior hepatic failure; prior hepatic encephalopathy;

Cardiovascular: New York Heart Association Class IV;

Respiratory: chronic restrictive, obstructive, or vascular lung disease resulting in severe exercise restriction; documented hypoxemia or hypercapnia; secondary polycythemia; severe pulmonary hypertension (>40 mmHg); ventilator dependence;

Renal: chronic hemodialysis;

Immuno-compromised: the patient has received therapy that suppresses resistance to infection including chemotherapy, radiation therapy, long-term or recent high-dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection (e.g. leukemia, lymphoma, AIDS)

Appendix 5: Data Collection Instructions

Patient Status Form:

1. **Check Trauma Database Excel document:**
   - Age
   - Sex
   - ISS
   - GCS
   - Hospital Admission Date
   - TBI status
   - Splenic injury
   - Hepatic injury
   - AIS
   - Injury type
   - Cause of injury (MVC, fall, etc.)

2. **Check EMG Nursing Notes:**
   - GCS: Under “Arrival” section, GCS score. Also written in “Presenting Complaints”. May be under “Initial Assessment”, History
   - Intubation Status: written in “Presenting Complaints”. Also under “Vital Signs”, FiO2
   - PRBC Transfusion: check under “Fluids Prior to Arrival”, under intake for PRBC. Make sure these are accounted for along with the PRBCs under “Transfusion Medicine” on vOACIS.

3. **Check Critical Care Flow Chart – Nursing Notes:**
   - Location immediately prior to ICU: Check Nursing Notes (third page of standard day), will state “Patient received from _____”. If patient was transferred from another hospital, check the EMG Nursing Notes, usually written under “Presenting Complaints”.

4. **Integrated Progress Notes:**
    - Check “ICU Admission Note” for Past Medical History and Antiplatelet Medication. Past medical history may not be entirely accurate, so check the “ICU Admission Note” and “ICU Progress Notes” to obtain the full past medical history. Pay special attention for any renal, liver, cardiac, respiratory diseases, immunodeficiencies and bleeding conditions.
    - ICU Admission Date: Use date of “ICU Admission Note”.
    - ICU Discharge Date: Check for “ICU Transfer Note”, and use the date of the note. Make sure that the transfer actually occurs on this day. Occasionally, the transfer is delayed for various reasons, and a new note is written a few days later. Can confirm the transfer by checking the Critical Care Flow Chart – Nursing Notes, under “Nursing Notes”. Nurses will indicate transfer occurred.

5. **Dead/Alive status:** At top of the patient main screen, the DOB is listed. If the patient is deceased, a **(D)** will be found next to the DOB. If death occurred while in the ICU, indicate “Death next to both boxes”. If death occurred while on a hospital ward following ICU discharge (this can be determined by reading the integrated progress notes), indicate Alive next to ICU discharge and Death next to hospital discharge.

Patient Daily Data Form:

1. **Bleeding: NUMBER OF DIFFERENT SITES TO CHECK FOR BLEEDING. MOST IMPORTANT COMPONENT OF THE DATA EXTRACTION. BE SURE TO COMPLETE CAREFULLY!!**

For all "Drainage" or "Secretions" lines, consider PINK, BLOOD-TINGED, SANGUINOUS, SEROSANGUINOUS, S, SS, MS, MPS to be bleeding.
For "Urine" color: consider PINK, RED-TINGED, RED, BLOOD-TINGED to be bleeding.
(Orange, tea-colored, concentrated are not considered bleeding)

Check Critical Care Flow Chart – Nursing Notes:

Critical care flow sheet

- Under "Neurological", check the "Drainage" line for drainage from surgical incisions or head drains. If bleeding is originating from an intracranial drain, consider this intracranial bleeding on the daily form
- Under "Respiratory", check Cough -> Secretions for bleeding. If the cough is "Spontaneous", the bleeding is considered hemoptysis. If the coughing is "Elicited", the bleeding is considered ETT/Trach Aspirate.
- Under "Respiratory", check CT#1 and CT#2 for bleeding. This is indicated as chest tube bleeding on the daily form.
- Under "Cardiovascular", check "Skin Integrity" -> "Drainage" -> Description for bleeding. "Sx incisions" indicates drainage from surgical incisions. These should be considered bleeding. Only consider bleeding from abrasions if severe (abrasions are very common and usually produce minimal bleeding.
- Under "Gastrointestinal", check "Drains" -> "Drainage" for bleeding. Indicate whether it is NG blood drainage, rectal bleeding (e.g. melena, hematochezia, etc.).
- Under "Genitourinary", check urine color. If considered bleeding, indicate the bleeding under "Other" on the daily form as "Hematuria".
- BE SURE TO CHECK EACH CRITICAL CARE FLOWSHEET FOR EACH DAY, ONE FOR EACH 12H SHIFT.

Nursing written notes:

- Read the nursing notes in entirety, checking for any bleeding. Pay special attention for the words/acronyms “SANGUINOUS”, “SEROSANGUINOUS”, PINK, BLOOD-TINGED, RED-TINGED, SS, S, MPS, MS.

Page containing resp rate:

- At bottom right corner of the page, there is a section containing the time, E Tube/T Tube Suction, Oral Suction. Check the “suction” boxes for any bleeding (SS, MS, etc.)

Page containing intake and output columns:

- Check right side of page under “OUTPUT” for any signs of bleeding.

Diagnostic Imaging:

- Check all CT/MRI scans for signs of bleeding.
- Check for embolization procedure to stop bleeding.
- Check Diagnostic Imaging -> Special for IVC filter insertion.

Operative Reports/Periops Record of operation:

- Quickly read over the operative report for “EBL” or Estimated Blood Loss. Often, a short paragraph is dedicated to this. It isn’t always indicated.
- Check the Output section in the Critical Care Nursing Notes for any procedure related bleeding.

Integrated progress notes:

- Check the “ICU Admission Note”, “ICU Progress Note”, “Trauma” notes, “Procedure Notes” for any signs of bleeding.
-

Determining the severity of a bleed (Major bleeding):

- If “hypovolemia” or hypovolemic shock was indicated in the integrated progress notes, or in the critical care nursing notes, and there is significant bleeding, indicate “life threatening bleed due to hypovolemic shock”.
- If bleeding is intracranial, pericardial or retroperitoneal, indicate it as a major bleed.

- If bleeding requires an invasive intervention (surgery, embolization, evacuation, etc.), indicate it as a major bleed.
- Check the Hgb values over the past 24 hours, and compare it to the previous day. If there is bleeding, and Hgb dropped by 20 or more, indicate as major bleed.
- Check Transfusion Medicine: If transfused 2 units of PRBCs or more (check the date/ time), in the 24 hours surrounding a bleed, indicate as a major bleed.
- Check the BP/HR graph in the critical care nursing notes. Check for any major decreases in BP and major increases in HR. Try to correlate the time that these occur with any major bleeds documented in the nursing notes or integrated progress notes. Take into consideration other factors which may affect BP and HR (fear, pain, anxiety, vasopressors, dehydration). If there is a major bleed, and the BP drops and the HR spikes around the same time or shortly before/after, indicate this under "Major Bleeding".

2. Remaining information on Daily Form:

- **Respiratory:** ET Tube or T-Tube, indicate "Invasive Mechanical Ventilation". If N/A under Artificial Airway, but CPAP is written somewhere in the "Respiratory Section", indicate "Non-Invasive Mechanical Ventilation" on the Daily Form.
- **Cardiovascular:** Check under Monitoring Catheters and IV Therapy. Compare it to the previous day. "PICC", any arterial line and any TLC are considered procedures. If no line on previous day, and new one on day of daily form, indicate it as if it has been inserted. Should also be indicated in the Nursing Notes and the Integrated Progress Notes. For "PICC" and "TLC" lines, indicate "Central Line Insertion", a 1 hour procedure. For arterial lines, indicate "Arterial Line Insertion", a 1 hour procedure.
- **Nursing Notes:** Read over, checking for bleeding, dialysis (IHD, CRRT, SLED), procedures, line insertions, mechanical ventilation, use of TEDs/SCDs, transfusion elements.
- **Vasoactive Infusion Drugs (under BP/HR chart):** Check for Norepinephrine, levophed, phenylephrine, neo-synephrine, dobutamine, dobutrex. If given, check off "vasopressor or inotrope infusion" on the daily form. Make sure that it indicates an amount next to the name (indicating that the infusion was actually given). If it indicates "off" for the entire 24 hour period, this means the infusion was not given.

- **Vascular Assessment:** under comments on the right, check for TEDs/SCDs. Indicate “Antiembolic stockings” for TEDs and SCDs on the daily form, respectively.
- **Medications:** Check for the following medications: Make sure the medications were actually given, indicated by a check mark at the time it was given.

Thromboprophylaxis or therapeutic use:

- Unfractionated heparin (UFH, heparin)

- Enoxaparin (Lovenox)

- Dalteparin (Fragmin)

- Tinzaparin (Innohep)

- Fondaparinux (Arixtra)

- Warfarin

If no prophylactic anticoagulation was given, indicate this and determine the reason why (integrated progress notes/critical care nursing notes). If the patient has any bleeding, indicate that it was because of this that the anticoagulant was not given. Can indicate multiple reasons (e.g. procedure and active bleeding). If cannot find a possible reason, indicate “possible oversight”.

Other anticoagulants:

- ASA/Aspirin (pay special attention in the elderly, and patients for which ASA was indicated in the PMHx on the status form)

- Clopidogrel (Plavix)

- Tranexamic Acid (Cyclokapron)

- Argatroban

- tPA (tissue plasminogen activator)

- TNK (tenecteplase)

Stress ulcer prophylaxis:

- Ranitidine (Zantac)
- Lanzoprazole (Prevacid)
- Pantoprazole (Pantoloc)

3. **Procedures:**
   - Check under Documents -> Operative Reports and Periops Record of Operation: write the procedure list that is indicated in the periops record of operation under "Procedures Performed".
   - For duration, take the time between "Surgery Started" and "Surgery Ended".
   - Other procedures of 1 hour duration:
     - **Central line insertion (TLC)**
     - **PICC insertion**
     - **Arterial line insertion**
     - **Tracheostomy**

   - Line insertion is determined based on nursing/integrative progress notes and day-day change in the Critical Care Flow Chart, under "Monitoring Catheters" and "IV Therapy".
   - Tracheostomy can be found in integrated progress notes/Critical care nursing notes, or under "Respiratory" in the Critical Care Nursing Notes, when ET-Tube changes to T-Tube.

   - Check diagnostic imaging for any interventional procedures (embolization, PEG insertion). Duration can be determine by the Critical Care Nursing Notes, based on the time the patient left the ICU for the radiology department, and when they return.
   - Check Critical Care Nursing Notes for any indication of procedures (bronchoscopy is often indicated here. For duration of bronchoscopy, time procedure is begun and ended is usually indicated).
   - Check Integrated Progress Notes for any "Procedure Notes".
   - Duration: Add total numbers of hours together. Input total duration into database.

4. **Laboratories: Check from 7am-7am. E.g. for the 26th of November 2011, check for values from 7am on the 26th, to 7am on the 27th. Choose the appropriate values (lowest or highest, see daily form).**

- Check the hematology values for HGB, PLAT, INR, PTT
- Check the biochemistry values for Blood pH, Creatinine, Fibrinogen, Lactate/Whole Blood Lactate.
- Check Transfusion Medicine for PRBCs, FFP, Platelets (buffy coat platelets, platelet apheresis, octaplex, factor VIIa, cryoprecipitate).

Appendix 6: Presence of Delayed Major Bleeding according to Severity and Location of Injury

	No Delayed Major Bleed (n=84) (%)	Delayed Major Bleed (n=66) (%)
Maximum AIS head		
minor	1 (1.2 %)	0 (0.0 %)
moderate	6 (7.1 %)	6 (9.1 %)
serious	7 (8.3 %)	3 (4.6 %)
severe	22 (26.2 %)	15 (22.7 %)
critical	21 (25.0 %)	30 (45.5 %)
unsurvivable	0 (0 %)	1 (1.5 %)
Maximum AIS neck		
minor	2 (2.4 %)	4 (6.1 %)
moderate	8 (9.5 %)	17 (25.8 %)
serious	5 (6.0 %)	1 (1.5 %)
unsurvivable	1 (1.2 %)	0 (0 %)
Maximum AIS chest		
minor	0 (0 %)	1 (1.5 %)
moderate	4 (4.8 %)	4 (6.1 %)
serious	19 (22.6 %)	16 (24.2 %)
severe	17 (20.2 %)	17 (25.8 %)
critical	2 (2.4 %)	4 (6.1 %)
Maximum AIS abdomen		
minor	1 (1.2 %)	0 (0 %)
moderate	14 (16.7 %)	12 (18.2 %)
serious	5 (6.0 %)	6 (9.1 %)
severe	2 (2.4 %)	7 (10.6 %)
critical	0 (0 %)	3 (4.6 %)
Maximum AIS extremity/pelvis		
moderate	10 (11.9 %)	12 (18.2 %)
serious	12 (14.3 %)	13 (19.7 %)
severe	3 (3.6 %)	10 (15.2 %)
critical	1 (1.2 %)	0 (0 %)
Maximum AIS external/ burn		
minor	16 (19.1 %)	10 (15.2 %)
severe	1 (1.2 %)	0 (0 %)

Appendix 7: Sample of Massive Transfusion Protocol used at The Ottawa Hospital