

**Developing an electronic hospital trigger for bleeding – The Ottawa
Hospital ETriggers project**

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ABSTRACT

Background

Bleeding can be an adverse side effect from hospital treatment. The aim was to develop an electronic identification method for patients who are bleeding within The Ottawa Hospital.

Methods

A retrospective exploratory cohort (N=1000) was used to identify potential candidate markers for bleeding. Electronic data were extracted to evaluate candidate identifiers. Data which were associated with bleeding events were assessed in a model derivation cohort (N=700). Multivariate analysis was used to establish the best model for identifying all bleeding events and in-hospital bleeding events.

Results

Overall 38% of the exploratory cohort had bleeding. In the model derivation set 29% had bleeding. The model predicting all bleeding included number of transfusions, admitting specialty, re-operation and endoscopy (C-statistic 0.82, 95%CI 0.79-0.86). The model predicting in-hospital bleeding included number of transfusions, admitting specialty and re-operation (C-statistic 0.78, 95% CI 0.73-0.84).

Conclusion

We have developed two models for identifying hospital bleeding events from The Ottawa Hospital electronic medical records. These should be validated prospectively on the hospital-wide population.

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ABBREVIATIONS

Abdominal aortic aneurysm	AAA
Agency for Healthcare Research and Quality	AHRQ
Area under the curve	AUC
Confidence interval	CI
Coronary artery bypass grafting	CABG
Hazard ratio	HR
Hemoglobin	Hb
International Classification of Disease	ICD
Interquartile range	IQR
Intraoperative	intraop.
Liters	L
Myocardial infarction	MI
National Surgical Quality Improvement Program	NSQIP
Non-ST segment elevation myocardial infarction	NSTEMI
Odds ratio	OR
Packed red blood cells	PRBC
Patient Safety Indicators	PSI
Percutaneous coronary intervention	PCI
Postoperative	postop.
Preoperative	preop.
Randomized control trial	RCT
Receiver operating characteristics	ROC
Red blood cell	RBC
ST segment elevation myocardial infarction	STEMI
Thrombolysis in myocardial infarction	TIMI
Total hip replacement	THR
Total knee replacement	TKR
United Kingdom	UK
United States	US

INTRODUCTION

Forward

At the outset of this thesis project, my remit was to develop an electronic method of identifying patients who were bleeding in The Ottawa Hospital. It became apparent during my literature search that no other hospital has developed or implemented such a tool. Furthermore, bleeding is an understudied medical topic, with no consensus definition and little epidemiological research.

To set the scene for the hospital ETrigger, my thesis introduction summarizes all published literature on the incidence of hospital bleeding, to demonstrate that bleeding is a common problem in hospital patients. I also summarized the research which demonstrates the association between bleeding and adverse outcomes (morbidity and mortality). Overall, the published research on bleeding is sparse and disparate, with no co-ordination between medical specialties. As a result there are many areas within medicine where there has been no bleeding research. I have brought the available evidence together, and acknowledge the research gaps.

In order to develop an identifier, I first had to establish a working definition of bleeding in medical, surgical and obstetrical patients. The introduction contains a summary of pre-existing bleeding definitions which provided the building blocks for the development of the study definition.

Patient safety

The role of hospital medicine has undergone fundamental changes in recent decades. There has been a transition of emphasis from inpatient centered, interventional care towards patient-physician partnership, with emphasis on quality of care and patient safety. Canadians have access to a comprehensive array of evidence based diagnostics and therapeutics. However health tests and treatments have co-existent benefits and unwanted side effects. Balancing these two aspects is the backbone of safe health care delivery.

Hospitals are large and complex organizations. Multiple departments are involved in everyday patient processing (patient registration, medical records, hospital wards, operating rooms, diagnostic imaging, laboratory analyses and informatics, to name a few). Each hospital domain employs hundreds or thousands of employees. Errors in patient care can occur in a range of places in the patient care pathway, and a decade ago might have gone undetected by the hospital or the patient. This meant that the same mistake could happen repeatedly, since no improvements were instigated to prevent future incidents. Highly publicized hospital lawsuits did not encourage employees to report medical errors for fear of blame. Furthermore, the traditional view of the doctor was that they would always act for the good of the patient, making it challenging to admit to mistakes. Paradoxically, medicine is actually a profession with high risk of error given the demands of clinical decision making, team leadership, long work hours, interrupted sleep and variable work shift patterns. In 1999 the Institute of Medicine in the United States (US) published a ground breaking report¹ which admitted that patient care in the US was 'not as safe as it should be', pointing out that preventable medical errors were not only costing lives but also money. Three years later the United Kingdom's Chief Medical Officer published a similar report² estimating that medical errors occurred in 1 in 10 hospital patients, and that unlike industry, the health system did not learn from its mistakes. In 2002 in Canada, the National Steering Committee on Patient Safety published the report 'Building a Safer System'³. These reports recommended a new open culture which did not apportion blame for mistakes, which nurtured research in the field of adverse medical events, encouraged standardized reporting of incidents and fed into large, established analytical systems.

Today it is generally accepted that integrating a learning system within a hospital is of benefit, allowing continual appraisal of the innumerable, complex systems in place for patient care. This enables constant improvement each time an unforeseen problem or threat comes to light. No system can eliminate medical error altogether, but all systems can be improved to contain or mitigate the adverse effects.

This is achieved by systematic analysis of all adverse outcomes, errors and threats to patient safety, in a 'no blame' culture. Hospital improvements are implemented with training and team commitment to safer health care.

Technology is advancing and we are living longer. As a result the way we practice medicine is constantly changing. Treatment for myocardial infarction (MI) is an example of this. Fifty years ago, a patient who was admitted to hospital with an MI would have the diagnosis made by electrocardiogram, would be prescribed aspirin and put on strict hospital bed rest for two weeks. Today, a similar patient has the diagnosis made by blood testing and coronary angiography, all within twelve hours of the onset of their symptoms. They are treated with dual antiplatelet therapy, with additional intravenous anticoagulation and intravenous antiplatelet therapy. They may well receive urgent percutaneous coronary stenting and in some instances go through coronary artery bypass grafting (CABG) surgery. Following this the patient is prescribed a β -blocker drug, a cholesterol lowering drug and is referred to a cardiac rehabilitation program which they attend on discharge from hospital a week later. Given the explosion of medical interventions and the accelerated pace of these interventions, it is not surprising that medical errors are common place. It is more important than ever that in the midst of this explosion, we do not lose sight of the goal to improve health without doing harm.

One recent literature review⁴ summarized preventable hospital adverse events into the following categories:

1. operation-related
2. anesthesia-related
3. drug-related
4. treatment-related
5. medical procedure-related
6. obstetric/postpartum
7. neonatal
8. fall or fracture
9. ward management
10. discharge-related
11. system processing
12. other medical error

The authors point out that several of the included studies associated adverse events with more than one category. Most events had multiple contributing factors. This has become the commonly accepted view of adverse events; that they are a culmination of systemic failings where multiple problems exist within a single patient's hospital journey.

Bleeding as an adverse event

Hospital adverse events often report on standardized incidents such as drug administration errors, surgical errors, and failure to prevent common hospital acquired complications like hospital acquired infection, venous thrombosis and pressure ulcers⁵. There are very few reports which include bleeding as an adverse hospital event or outcome. Traditionally, bleeding was accepted as part of many disease processes, without thought to whether the bleeding could be averted. For example, it would not be possible to perform surgery without some degree of blood loss since cutting through the skin and body tissues causes instant small vessel injury. Peptic ulceration of the stomach or duodenum is frequently diagnosed when a patient presents to hospital with hematemesis, at which point the ulcer has eroded through the wall, into a blood vessel. The diagnosis of an intracranial bleed is the starting point in a process of neurosurgical intervention and rehabilitation. In the past, the treating physician may have recognized that bleeding was associated with the use of aspirin or an anticoagulant, however may not have considered it their place to feed this back to the specialist or family physician who prescribed the medication. Nor would the information have been collected in a hospital or regional information system. In other words, hospitals were geared towards treating disease and dealing with disease complications as they arose, rather than processing this information to help mitigate complications in future patients. In recent years there have been a few compelling research studies which demonstrate the relationship between bleeding and certain interventions: antiplatelet medication⁶, anticoagulant medication⁷, surgery⁸ and procedures such as coronary intervention⁹. In addition, we repeatedly see the same patient demographic associations such as renal failure, older age and low body mass index. For the first time, bleeding has been placed in the hospital adverse events category as a recognized complication of treatment, and can be viewed in part as an iatrogenic illness. Furthermore, sparse research has started to quantify the precise bleeding risk of hospital interventions, and to identify patients who are at particular risk of bleeding.

Bleeding has become a topical issue and publications on bleeding have increased year by year (Figure 1). High risk specialties such as surgery and cardiology are increasingly aware that successful treatment not only depends on correction of the underlying disease, but also on intervention without serious iatrogenic illness such as bleeding.

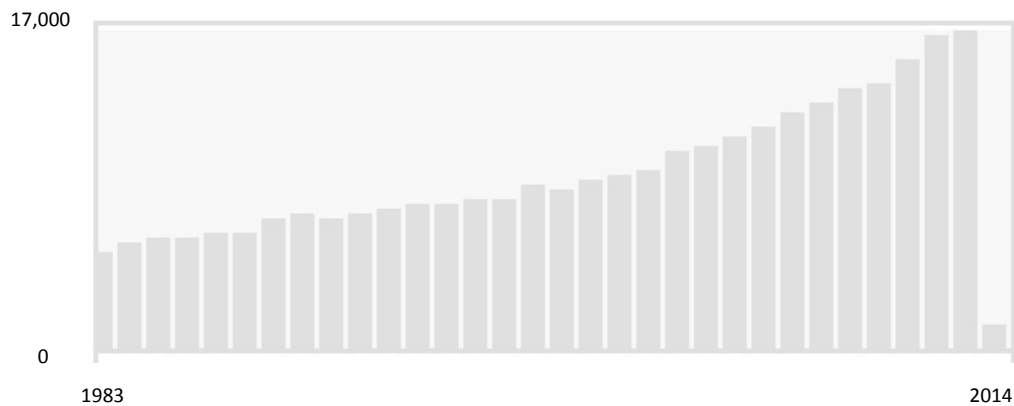


Figure 1: Archiving of publications on 'bleeding' in PubMed.gov over time.

Each bar represents a successive year.

<http://www.ncbi.nlm.nih.gov.proxy.bib.uottawa.ca/pubmed/?term=bleeding>

In summary, bleeding might be viewed as an iatrogenic adverse event which can complicate medical treatments.

Why is bleeding an adverse event?

Blood is the delivery system for oxygen and nutrients to the body's tissues, and for carbon dioxide and waste product elimination. Our bodies carry around 5 litres (L) of blood, which means that even small blood losses of less than a litre can impact on cell function and waste removal. Intuitively, we know that blood loss is not a good thing. Even lay people are familiar with the phrase 'to bleed to death'. However, when we search the research literature, there is a dearth of publications specifically assessing the risk of bleeding.

Bleeding and the risk of death

Bleeding in acute coronary syndrome

MI is routinely treated with aspirin and heparin. In addition, these patients frequently undergo percutaneous coronary intervention (PCI) which involves catheterization of a major artery and instrumentation of the coronary arteries while receiving large doses of both antiplatelet and anticoagulant drugs. Two studies have quoted the rate of in-hospital bleeding post MI as 7% and 12%^{10;11}. Both studies showed that bleeding was associated with a higher 30 day mortality rate, with hazard ratios (HR) of 6.2 and 1.3 respectively.

The TIRTON-TIMI 38 study¹² randomized 13,608 patients with ST segment elevation MI (STEMI) to either aspirin + prasugrel or aspirin + clopidogrel prior to PCI. By the TIMI criteria, 4% had a major bleed which was associated with a HR for death of 5.8. Patients who had intracranial bleeding were at a higher risk of death (65% died) compared to extra-cranial bleeding (where 14% died). The ExTRACT-TIMI 25 study¹³ randomized 20,323 STEMI patients who were offered thrombolysis rather than PCI to either enoxaparin or unfractionated heparin anticoagulation. Thirty day mortality rates were 38%, 10% and 7% for major bleeding, minor bleeding and no bleeding. Pooled analysis of 7 PCI randomized control trials (RCTs)¹⁴ showed that although intervention catheter site bleeding was a weaker predictor of 1 year mortality compared to non-access site bleeding (4.5% versus 10.0%), both were significant predictors independent of age, diabetes, renal function and cardiac failure.

Bleeding in surgery

An analysis of the American College of Surgeons National Surgical Quality Improvement Program database which included 970,593 patients undergoing surgery in 200 hospitals¹⁵ categorized patients by the number of red cell transfusions they had received. Blood transfusion is a common treatment for significant blood loss during surgery, therefore it is likely that patients receiving more than four transfusions had experienced large blood loss during surgery. Among the patients who were not transfused (n=917,651), there was a 1.2% 30 day mortality rate. For those who received between 1 and 4 units packed red blood cells (PRBC) (n=45,457), 30 day mortality was 8.9% and among those who received more than 4 (n=7,485), 30 day mortality was 21.5%. Of course, this evidence is limited by the assumption that those who were transfused had no other indication for blood transfusion, such as preoperative anemia, or other acquired postoperative anemia.

A different analysis of the same data¹⁶ linked bleeding requiring 5 units PRBC or more postoperatively with cardiac arrest in hospitalized surgical patients. Following cardiac arrest, 70% died within 30 days. The bleeding episodes were identified prior to cardiac arrest in almost 90% of cases.

Major bleeding after cardiac surgery has an odds ratio (OR) for death at 30 days of 3.5¹⁷ and gastrointestinal (GI) complications post coronary artery bypass grafting (CABG) surgery (almost exclusively bleeding) increase mortality by 13 times¹⁸.

In a retrospective cohort of 525 patients who underwent endovascular aortic repair for aortic aneurysm¹⁹, 8% were estimated to have lost 1-2 L blood in the operating room, 4% between 2 and 5 L blood in the operating room and 2%, greater than 5 L (equivalent to their total circulating volume). Bleeding greater than 2 L was associated with death at 30 days (OR 30.8).

Bleeding in treatment of venous thromboembolism

In venous thromboembolism patients^{20;21}, analysis of the RIETE database demonstrated that 23% of all patients who experience a major bleed, died from the bleed and the ZATPOL registry²² found that major bleeding was an independent predictor of 90 day mortality following diagnosis of PE.

Bleeding from the gastrointestinal tract

The risk of death from peptic ulcer bleeding is increased by the presence of cancer, liver disease and renal disease²³ and the Danish national registry²⁴ reports a 30 day mortality rate from peptic ulcer bleeding of 11% which has remained constant from 2004 till 2011.

Bleeding and the risk of cardiac event

The POISE study²⁵ prospectively followed 9048 patients undergoing non-cardiac surgery and documented the rate of perioperative myocardial infarction. Five percent of patients had a perioperative MI and bleeding requiring 2 or more units of blood was an independent predictor of MI (OR 3.6).

Bleeding and the risk of acute kidney injury

A Japanese study of 2646 patients undergoing PCI showed that the size of the drop in hemoglobin post PCI relates to both the incidence of bleeding and the incidence of acute kidney injury²⁶. In the group who had a drop of >30g/L, there was a 25% incidence of acute kidney injury. Patients with <10g/L drop had a 6% incidence of acute kidney injury.

Bleeding and the duration of hospitalization

A French national database analysis²⁷ identified all surgeries coded for both secondary hemostasis and blood transfusion. The highest rates were found in cardiac, vascular, orthopedic and transplant surgery. Those identified as having postoperative bleeding had on average a 3 day longer hospital stay at a cost of an additional €2000.

Additional factors associated with bleeding

Many bleeding events occur in patients who are being treated with medications which prevent thrombosis, such as anticoagulants (warfarin, heparin, rivaroxaban, dabigatran and low molecular weight heparin) and antiplatelets (aspirin, the adenosine diphosphate receptor inhibitors clopidogrel,

prasugrel, ticagrelor and the glycoprotein IIB/IIIA inhibitors abciximab, tirofiban and eptifibatide). These treatments are used intensively in cardiology, cardiac surgery, vascular surgery and thrombosis, because such patients are at risk of forming a fatal thrombosis. Unfortunately the drugs also exacerbate bleeding, and the normal approach would be to hold one or all of these medications during a bleeding event, since the risk-benefit balance of anticoagulant and / or antiplatelet medication changes to greater risk than benefit. Therefore it is not surprising that one consequence of bleeding is clotting, which manifests as deep vein thrombosis, pulmonary embolism, stroke or MI. This was demonstrated in the PARIS registry which followed 5018 patients taking dual antiplatelet therapy following PCI stent insertion²⁸. Patients were followed for 2 years. Unplanned interruption of the dual therapy (either because of bleeding or the patient's own decision) was associated with an increased risk of major adverse coronary event (cardiac death, stent thrombosis, MI or revascularization). The risk was the greatest during the first 7 days of discontinuation, when the HR was 7. The same has been observed with in-hospital bleeding following STEMI²⁹.

In summary, a bleeding event increases the risk of death, renal failure, MI, and thrombotic complications.

The epidemiology of bleeding in hospitals – how big a problem is it?

A systematic review of the literature reveals surprisingly little research on the incidence of in-hospital bleeding. The majority of work has been reported on cardiac surgery, where bench marking and monitoring have been routine for the past decade. Unlike other surgeries, bleeding from cardiac surgery can result in death, with only a few hundred milliliters of blood lost into the pericardial space. Furthermore, large volumes of blood can collect rapidly into the pleural spaces, and patients may bleed to death relatively quickly. It is not surprising that cardiac surgery was the first to set safety standards for patient care. Cardiology is the second most common specialty publishing on bleeding. The last two decades has produced hundreds of trials on cardiac patients, however bleeding only became recognized as an important primary outcome in interventional cardiology recently, and the majority of papers report the incidence of bleeding as a secondary or safety outcome in older RCTs.

Tables 1 to 6 display the results of studies reporting the incidence of in-hospital bleeding. Table 1 shows a summary of studies detailing blood loss in major hip and knee surgery. There are varying reports on the prevalence of blood transfusions, however it appears the calculated blood loss is large, and lies in the region of 2000ml. None of these studies help in determining the acceptable amount of blood loss during orthopedic surgery, nor do they shed light on a definition for 'too much blood loss', since it appears that blood loss is a normal part of the procedure. Table 2 shows the results of studies reporting blood loss during cardiac surgery. As with orthopedic surgery, blood loss is expected in cardiac surgery and the papers concord that there is sizable blood loss during surgery (seen by measured blood loss and blood transfusions during surgery), and after surgery (measured by chest tube drainage, re-operation for bleeding and blood transfusion). In general, it appears that blood loss in cardiac surgery may be greater than in orthopedic surgery, although only one paper compares both entities⁸. Table 3 shows reported bleeding after colonoscopic polypectomy or cancer dissection. The results were quantified in a binary format: bleeding present or absent. No study gave estimates of volume of blood loss, and gastroenterologists appear to concord that bleeding following polypectomy is an adverse occurrence. I found only one paper on general (laparoscopic) surgery and another on vascular (aortic aneurysmal repair) surgery. The analysis of 14,243 laparoscopic surgeries (cholecystectomy, appendectomy, herniotomy, fundoplication, colon resection and lysis of adhesions) reported a 1 in 200 rate of re-operation for bleeding, which seems higher than expected. The database is over 15 years old, so it is difficult to know whether this is reflective of today's practice.

Table 1: Major orthopedic surgery					
Authors	Study	Cohort	Groups	Outcome	Result
⁸ Gombotz et al. Austria 2007	Prospective multicentre cohort	1401 THR 1296 TKR	THR TKR	% RBC volume loss % patient given PRBC % RBC volume loss % patient given PRBC	37% 43% 35% 41%
³⁰ Rosencher et al. France 2003	Prospective international multicentre cohort	2640 THR 1305 TKR	THR TKR	Median calculated blood volume loss Median calculated blood volume loss	1944 ml 1934 ml
³¹ Oberweis et al. USA 2013	Retrospective analysis	3082 patients undergoing hip, knee and spinal surgeries	All patients	Any transfusion >1 unit in postoperative period ICD coded as bleed	25% 5% 1%
³² Irisson et al. France 2013	Retrospective analysis, before-after case series	451 patients undergoing THR and TKR	Intraop. tranexamic acid No tranexamic acid	Calculated blood volume loss Calculated blood volume loss	1260ml 1900ml
³³ Kragh et al. Sweden 2011	Retrospective analysis of different RCT	255 hip fracture patients	Aspirin N=118 No aspirin N=137	% given blood transfusion % given blood transfusion	63% 54%
One study ³⁴ on hip fracture surgery was not included in table because they reported the surgeons estimated blood loss only.					

Abbreviations for tables 1 to 7: Total hip replacement (THR), total knee replacement (TKR), intraoperative (intraop.), international classification of disease (ICD), preoperative (preop.), red blood cells (RBC), packed red blood cell units (PRBC), non-steroidal anti-inflammatory (NSAID), non-ST segment elevation MI (NSTEMI), Thrombolysis in myocardial infarction study (TIMI), hemoglobin (Hb), coronary artery bypass grafting (CABG), ST-segment elevation myocardial infarction (STEMI), percutaneous coronary intervention (PCI)

Table 2: Cardiac surgery					
Authors	Study	Cohort	Groups	Outcome	Result
⁸ Gombotz et al. Austria 2007	Multicentre prospective cohort study N=777	CABG patients	All patients	% RBC volume lost % patients transfused	45% 55%
³⁵ Deja et al. Poland 2012	Prospective RCT N=789	CABG patients <age 75	Preop. aspirin Preop. placebo	>750ml bleed in 12 hours >1L total bleed Return to OR >750ml bleed in 12 hours >1L total bleed Return to OR	22% 34% 5% 14% 24% 4%
³⁶ Jacob et al. USA 2012	Retrospective registry N=1016 propensity matched	CABG + valve replacement	Aspirin stopped >5 days preop. Aspirin within 5 days preop.	% transfused intraop. % transfused postop. Return to OR % transfused intraop. % transfused postop. Return to OR	45% 42% 3.7% 43% 49% 6.1%
³⁷ Miceli et al. UK 2012	Retrospective registry N=926	CABG patients prescribed aspirin and clopidogrel	Both given preop. Either aspirin or clopidogrel preop. Both held preop.	Return to OR Chest tube drainage Mean PRBC units Return to OR Chest tube drainage Mean PRBC units Return to OR Chest tube drainage PRBC units	4.5% 761ml 0.8 2.9% 720ml 0.5 1.2% 687ml 0.3
³⁸ Maltais et al. Canada 2008	Retrospective analysis of off-pump CABG patients N=453	Normally takes clopidogrel No clopidogrel	Clopidogrel No clopidogrel	Mean intraop. blood loss Postop. chest drainage Mean intraop. blood loss Postop. chest drainage	702ml 865ml 554ml 604ml
³⁹ Al-lawadi et al. Oman 2012	Retrospective analysis of CABG by one surgeon N=109	Aspirin stopped <1 week preop. Aspirin stopped >1 week preop.	Aspirin preop. Aspirin held	Mean postop. chest drainage first 12h % patients transfused postop. Mean postop. chest drainage first 12h % patients transfused postop.	447ml 84% 357ml 74%

Table 3: Colonoscopic polypectomy and upper endoscopy					
Authors	Study	Cohort	Groups	Outcome	Result
⁴⁰ Manocha et al. USA 2012	Retrospective analysis N=1174	Polypectomies	Patients taking aspirin or NSAID N=502	Reported bleeding	3.2%
			Not taking aspirin or NSAID N=672	Reported bleeding	3.0%
⁴¹ Singh et al. USA 2010	Retrospective analysis N=1385	Polypectomies	Patients taking clopidogrel N=142	Immediate bleed Late bleed	1.2% 1.0%
			Not taking clopidogrel N=1243	Immediate bleed Late bleed	1.2% 3.5%
⁴² Gandhi et al. Canada 2013	Meta-analysis of cohort studies	Polypectomies	Continued clopidogrel therapy	Immediate bleed Late bleed	5.1% 2.7%
			Controls (no clopidogrel)	Immediate bleed Late bleed	1.7% 0.6%
⁴³ Inoue et al. Japan 2013	Retrospective cohort N=117	Polypectomies	Patients usually anticoagulated N=45	Reported bleeding	20%
			No anticoagulation N=72	Reported bleeding	1.4%
⁴⁴ Matsumoto et al. Japan 2012	Retrospective cohort N=375	Endoscopic colonic tumour resection	All patients	Post-resection bleeding requiring repeat colonoscopy	4.5%

Table 4: General surgery					
Authors	Study	Cohort	Groups	Outcome	Result
⁴⁵ Schafer et al. Switzerland 2000	Database of laparoscopic general surgeries 1995-1997 N=14,243	Laparoscopic surgeries	All patients	Intraoperative bleeding Bleeding within 24h postop. Re-operation for bleeding	2.3% 1.8% 0.5%

Table 5: Vascular surgery					
Authors	Study	Cohort	Groups	Outcome	Result
¹⁹ Montán et al. Sweden 2013	Retrospective cohort N=525	Endoscopic abdominal aortic aneurysm repairs	All patients	Blood loss as recorded on the anesthesiologist chart <1000ml 1000-2000ml 2000ml-5000ml >5000ml	86% 8% 4% 2%

Table 6: Bleeding post coronary event					
Authors	Study	Cohort	Groups	Outcome	Result
¹² Hochholzer et al. USA 2011	TIRTON-TIMI 38 N=13,608	STEMI patients awaiting PCI	All patients	TIMI major bleeding - caused by instrumentation - caused by trauma - spontaneous	4.0% 1.7% 0.3% 2.0%
¹³ Giugliano et al. USA 2010	EXTRACT-TIMI 25 N=20,323	STEMI patients treated with thrombolysis	All patients	TIMI major bleeding	1.5%
⁴⁶ Kirtane et al. USA 2006	PROTECT-TIMI 30 N=567	NSTEMI patients having PCI	All patients	TIMI major bleeding TIMI minor bleeding	0.7% 2.5%
⁹ Subherwal et al. USA 2012	CathPCI registry 2005-2009 N=1,708,449	Patients undergoing PCI	Elective PCI STEMI NSTEMI	Bleeds requiring transfusion or drop Hb 30g/L or access site hematoma	2005 1.4% 2009 1.1% 2005 4.9% 2009 4.0% 2005 2.3% 2009 1.8%
⁴⁷ Rubboli et al. Italy 2013	War-stent registry N=411	Patients on warfarin undergoing PCI	All patients	In-hospital TIMI bleeding	2.1%
⁴⁸ Andrade et al. Canada 2013	Meta-analysis of pre-2010 retrospective cohort studies	Patients on triple therapy for coronary stent	All patients	Post PCI in-hospital bleeding	1.6%
²⁹ Boden et al. Netherlands 2013	Retrospective cohort N=963	STEMI patients having PCI	All patients	In-hospital bleeding as defined by GUSTO TIMI BARC CRUSADE	1.3% 6.9% 8.2% 21.0%
⁴⁹ Ndrepepa et al. Germany 2012	Data from 6 RCTs N=12,459	Patients undergoing PCI	All patients	Bleeding as defined by TIMI BARC	3.0% 9.9%

Table 6 continued: Bleeding post coronary event					
⁵⁰ Subherwal et al. USA 2009	Retrospective multicenter cohort N=89,134	NSTEMI patients	All patients	In-hospital bleeding defined by CRUSADE	9.6%
⁵¹ Abu-Assi et al. Spain 2010	Retrospective cohort N=782	NSTEMI patients	All patients	In-hospital bleeding defined by CRUSADE	9.5%

Table 6 demonstrates how results can change, depending on the patient cohort and the definition of bleeding. Reported bleeding during treatment for acute coronary syndrome varies from 1.5% when the 'Thrombolysis In Myocardial Infarction' (TIMI) definition is applied, to up to 20% when the 'Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines' (CRUSADE) definition is applied. Bleeding definitions can be found in Table 7. Furthermore, the bleeding rates for patients treated for STEMI are consistently higher than those reported for non-ST segment elevation MI (NSTEMI) and elective PCI.

Less is known about general medical patient in-hospital bleeding. Analysis of the 15,206 patients in RIETE database²⁰ showed that 1.6% of patients diagnosed with venous thrombosis had a major bleed within 3 months. An earlier RIETE analysis²¹ (of 24,395 patients) had reported the rate to be 2.2%. The ZATPOL database is a national Polish database of patients investigated for pulmonary embolism in 2007 - 2008. Of 1112 patients diagnosed with pulmonary embolism, 3.6% had in-hospital bleeding and 0.5% died of their bleed²². Cardiology and thrombosis patients are treated with full dose anticoagulation and are inherently at high risk of bleeding, however less is known about other medical patients, who may be frail with comorbidities predisposing to in-hospital bleeding. There have been medical RCTs looking at the efficacy of venous thromboembolism prophylaxis. Each study recorded the rate of bleeding as a safety outcome, and the studies varied in their definitions of bleeding. A recent meta-analysis⁵² recorded the rate of bleeding within 3 months of administration of prophylaxis as between 3% (in patients given no prophylaxis) and 6% (with prophylaxis). So it appears that this relatively understudied problem affects a significant number of hospitalized medical patients.

In summary, bleeding is a common occurrence in cardiac and orthopedic surgery. It is an adverse event following gastrointestinal polypectomy and is a common adverse event in treatment for MI. Little is known about the incidence of bleeding in general medical patients and patients admitted to other surgical specialties.

The definition of bleeding

As we saw in Tables 1 to 6, studies have used different ways to determine whether a bleeding event occurred. This makes synthesis of the published literature almost impossible, since each study is reporting on a different outcome. We can also conclude that blood loss is an integral and normal part of surgery, which makes it harder to define abnormal blood loss in surgery.

What are the candidate bleeding definitions?

Surgical patients

The surgical pathway can be broken down into the preoperative period, intraoperative period and postoperative period. It would be inaccurate to count bleeding in the preoperative period as 'operative bleeding', however, there is evidence to suggest that blood loss from surgery does not stop when the skin is closed. A French cohort study³² documented that 75% of the total blood loss occurs within 24 hours of orthopedic surgery, and that a further 20% of blood loss occurs between 24 and 72 hours after surgery. This blood loss occurs into the tissues surrounding the surgical bed, and unlike intraoperative loss, is difficult to quantify. Therefore it seems reasonable to determine 'perioperative' blood loss rather than simply 'intraoperative' blood loss as occurring between the start of surgery and 72 hours after surgery.

Traditionally, intraoperative blood loss is estimated by the surgeon, who determines the amount of blood loss from suction drainage and visual inspection. Surgeon estimated blood loss has been shown to consistently underestimate the volume of blood lost³⁰, therefore does not seem an ideal candidate definition.

Death from bleeding is a hard, binary outcome, however we would like to identify patients who suffer morbidity as well as mortality from bleeding. Re-operation is another hard outcome, however repeat surgery entails further blood loss in the process of obtaining hemostasis, and can somewhat compound the problem. Although re-operation is an easily defined outcome, it is also a late result of bleeding. It would be optimal to intervene when a more subtle degree of blood loss is detected, in order to prevent bad outcomes such as death and return to the operating room.

Cardiac surgeons frequently determine bleeding by the amount of blood drained by the chest drain, in terms of the bleeding rate (ml/kg/hr)⁵³. The amount of blood drained within three hours of surgery can

determine whether the surgeon requires to re-operate as an emergency. Although surgical site drains are common place in other types of surgery, drainage is seldom used to identify perioperative bleeding. The prescription of PRBC transfusion could be another way to define whether a patient is bleeding, however blood transfusions are used to treat long standing, symptomatic anemia as well as bleeding. There is also variation in the prescription of blood transfusion for bleeding patients, with different physicians using different hemoglobin transfusion thresholds. From the information on the above tables, it seems that blood transfusion is a routine part of many surgeries and considered a normal part of some procedures. In fact, some surgeries would not be performed if transfused blood were not available.

A literature review was performed to search for definitions of in-hospital bleeding. The results are displayed in Tables 7 and 8.

Table 7: Comparison of standardized bleeding definitions for cardiac patients		
Bleeding Academic Research Consortium (BARC) ⁵⁴	Type 0	No bleeding
	Type 1	Bleeding that is not actionable and does not cause the patient to seek medical advice or intervention, may include episodes leading to self-discontinuation of medical therapy
	Type 2	Any overt, actionable hemorrhage that does not fit the criteria for type 3, 4, or 5 but requires nonsurgical, medical intervention by a healthcare professional, causes hospitalization or prompts evaluation
	Type 3a	Overt bleeding with hemoglobin drop of 30-50g/L Any transfusion with overt bleeding
	Type 3b	Overt bleeding plus hemoglobin drop of 50 g/L Cardiac tamponade Bleeding requiring surgical intervention for control Bleeding requiring intravenous vasoactive agents
	Type 3c	Intracranial hemorrhage Intraocular bleed compromising vision
	Type 4 CABG-related bleeding	Perioperative intracranial bleeding within 48 h Re-operation for bleeding Transfusion of 5 units PRBC within a 48 h period Chest tube blood output >2L within a 24-h period
	Type 5a	Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
	Type 5b	Definite fatal bleeding Overt bleeding or autopsy or imaging confirmation

Table 7 continued: Comparison of standardized bleeding definitions for cardiac patients		
Thrombolysis in myocardial infarction (TIMI) ⁵⁵	Major	Intracranial bleeding Hemorrhage associated with a drop in hemoglobin of 50 g/L Fatal bleeding
	Minor	Overt bleeding resulting in hemoglobin drop of 30-50 g/L
	Requiring medical attention	Any bleeding not meeting 'major' or 'minor' criteria which requires an intervention, requires an unscheduled healthcare visit or prolongs admission
	Minimal	Overt bleeding not meeting the three above criteria
	CABG associated bleeding	Fatal bleeding Intracranial bleeding Re-opening of chest for bleeding Transfusion of 5 or more units PRBC within 48 hours >2L blood drainage via chest tube in 24 hours
Global Use of Strategies to Open Occluded Arteries (GUSTO) ⁵⁶	Severe	Intracerebral bleeding Causing hemodynamic compromise
	Moderate	PRBC transfusion given but no hemodynamic compromise
	Mild	Bleeding that does match either 'severe' or 'moderate'
Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines (CRUSADE) ⁵⁰	Major bleeding	Intracranial hemorrhage
		Documented retroperitoneal bleed
		Hematocrit decrease $\geq 12\%$
		PRBC transfusion when baseline hematocrit $\geq 28\%$
		PRBC transfusion when baseline hematocrit $< 28\%$ with witnessed bleed

It can be appreciated that not all 'major bleeds' are the same thing. For example, the TIMI definition requires a hemoglobin drop of 50 g/L, death or intracranial bleeding, and the CRUSADE definition only requires a drop in hematocrit of 12% or else a single blood transfusion. The GUSTO criteria are a little more open to interpretation, so that a large retroperitoneal bleed which accumulates over several days and does not cause hypotension, but requires surgery and blood transfusion could be classified as a moderate rather than a severe bleed. The BARC consortium have attempted to get around this by separating types of bleeding into different categories, rather than trying to measure all with one

measuring scale. The BARC definition gives a more descriptive bleeding definition, rather than a single percentage.

It is interesting that the BARC consortium opted to use the same definition of CABG related bleeding as the original TIMI definition. As yet, no published cardiac surgery study has used this definition to determine perioperative bleeding which asks the question whether a score derived by cardiologists is helpful in defining bleeding in cardiac surgery.

There has been little research on bleeding definitions for other medical and surgical patients. In the past decade the International Society of Thrombosis and Haemostasis have derived universal definitions for both (Table 8).

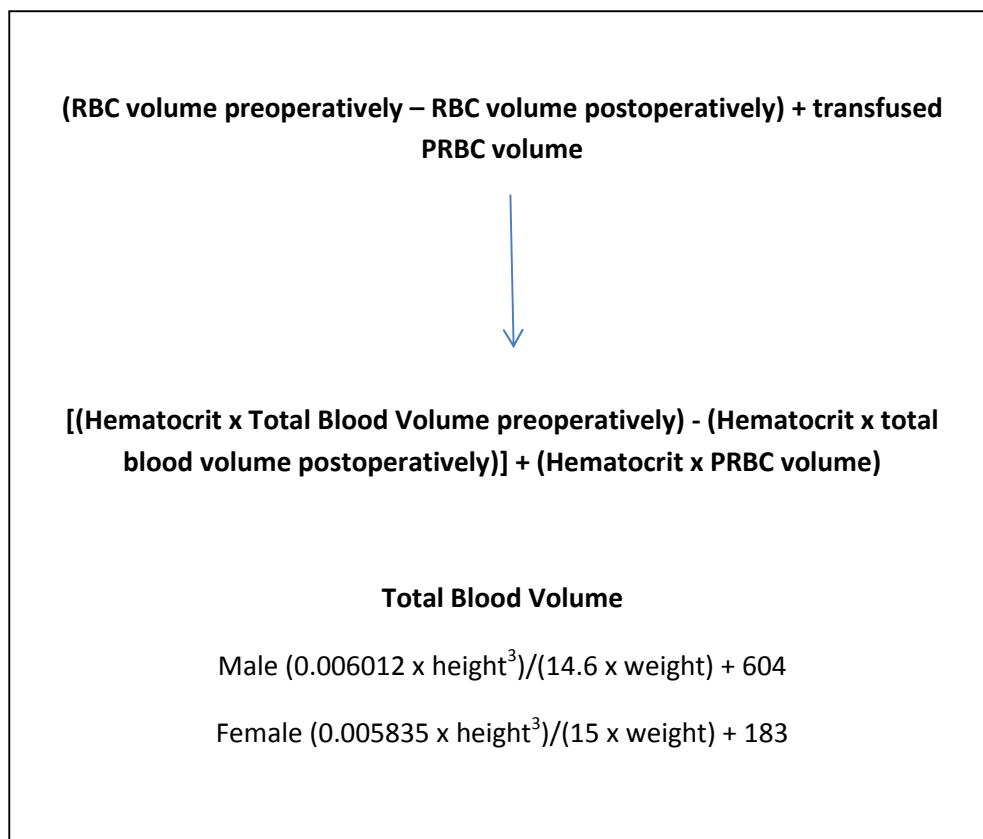
Table 8: Standardized bleeding definitions for all patients		
International Society of Thrombosis and Haemostasis (ISTH)	Major bleeding in surgical patients ⁵⁷	Fatal bleeding
		Symptomatic bleeding in a critical area or organ (intracranial, intra-spinal, intraocular, retroperitoneal, pericardial, in a non-operated joint, or intramuscular with compartment syndrome) assessed in consultation with the surgeon
		Extrasurgical site bleeding causing a fall in hemoglobin level of 20 g/L or more, or leading to transfusion 2 or more units PRBC, within 24–48 h of the bleeding
		Surgical site bleeding that requires a second intervention, or hemarthrosis which interferes with rehabilitation or results in prolonged hospitalization, or a deep wound infection
		Surgical site bleeding that is unexpected and prolonged, sufficiently large to cause hemodynamic instability, as assessed by the surgeon. There should be an associated fall in hemoglobin level of >20g/L or transfusion 2 or more units PRBC within 24 h of bleeding.
International Society of Thrombosis and Haemostasis (ISTH)	Major bleeding in non-surgical patients ⁵⁸	Fatal bleeding
		Symptomatic bleeding in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome)
		Bleeding causing a fall in hemoglobin level of 20 g/L or more, or leading to transfusion 2 or more units PRBC

The ISTH has a more encompassing definition of major bleeding in that it only requires a drop in hemoglobin of 20g/L, and is likely to identify a greater number of major bleeding events than the cardiac definitions. The ISTH definitions have their limitations:

1. The definitions were developed for use in future prospective anticoagulation studies and include consultation with the surgeon. They were not derived to be useful for retrospective analyses.
2. The definition of surgical bleeding relies on the surgeon identifying that the patient has had excessive bleeding. Given that we know surgeons consistently underestimate the volume of blood loss, it remains to be seen whether the method is sensitive in the detection of major bleeding.

One survey has published the outcomes from 100 orthopedic surgeons in the US, UK, France, Germany and Spain⁵⁹ (500 total). Surgeons were more concerned about bleeding causing re-operation than extra-surgical site bleeding, or bleeding leading to transfusion or anemia. Few surgeons had read the definitions of bleeding in published articles and many found the definitions confusing. Overall there seemed to be a higher weight assigned to surgical site bleeding than other types.

How do studies determine the actual volume of blood lost?



The only way to estimate the true volume of blood lost during surgery is to calculate the circulating blood volume before and after surgery. This too is an estimation which is based on the patient's weight and height. The calculation requires that the patient has blood drawn for a blood count pre-surgery and 5 days post-surgery. Blood lost is equal to the preoperative volume minus the postoperative volume plus the transfused volume. I found no publications suggesting that the formula is used routinely on a hospital ward.

There is no standard definition for bleeding. Many studies have classified bleeding events by their severity (major versus minor). Such classifications are lacking in description of bleeding type, for example stroke, operative bleeding and gastrointestinal bleeding. Furthermore, the existing definitions vary considerably in their threshold for recognizing an event and definition of serious bleeding.

Risk of transfusions

The practice of administering blood transfusion has changed over the past decades, driven in the main by high profile litigation over the transmission of hepatitis B and C virus, as well as HIV. Changes to donor screening have reduced the rates of transmission to less than 1 in 200,000⁶⁰. Other risks of blood transfusion include error leading to blood group incompatibility, transfusion related acute lung injury, hemolysis, and death. Death from transfusion is currently estimated to occur less than 1 in 2 million transfusions⁶⁰. With careful and safe transfusion practices, blood transfusion has become a safe treatment.

In the past decade, new concerns have arisen about the safety of blood transfusions. Theoretically, blood transfusions replace normal, healthy blood with old, stored blood. 2,3 diphosphoglycerate is present in normal red blood cells and promotes the release of oxygen in hemoglobin to the tissues. Transfused blood is depleted in 2,3 diphosphoglycerate and the red blood cells are less able to donate their oxygen to the body's tissues. Although donated blood can carry oxygen, the oxygen cannot be accessed in the usual way by the recipient's tissues, and the blood is unable to provide a vital function. This is demonstrated by a 'left shift' in the hemoglobin dissociation curve.

Furthermore, white blood cells in stored blood produce cytokines, key mediators in inflammatory processes. Therefore transfused blood may provide an inflammatory load to patients who already have a degree of inflammation following surgery or a bleeding diathesis.

It is normal practice to use the hemoglobin or hematocrit as a guide for evaluating the need for blood transfusion. When hemoglobin drops below a critical level, most physicians would consider that the oxygen delivery system is failing and would prescribe a blood transfusion. However, taking into account the altered nature of stored, donated blood, it is unclear whether this practice actually benefits patients. For example, it might be possible that the oxygen dissociation curve of the transfused blood is so 'left shifted' that the transfused red blood cells draw the oxygen out of the bodily tissues, and compounds their illness by exacerbating tissue hypoxia.

Certainly, it has been demonstrated that preoperative anemia is associated with worse postoperative outcomes. Wu et al.⁶¹ studied data on over 300,000 elderly veterans who had noncardiac surgery between 1997 and 2004. For every 1% decrease in the preoperative hematocrit there was a 1.6% increase in the risk of death after surgery. Worsening degrees of anemia were also related to higher rates of postoperative MI. In 2005, Sabatine et al. analyzed the data from 16 TIMI acute coronary syndrome trials⁶², showing again that the degree of anemia on admission predicted cardiovascular

mortality and adverse cardiovascular events. However neither of these studies show that treatment of the anemia with red cell transfusion prevents death.

Loor et al. analyzed data from 7942 patients having cardiac surgery⁶³ and found that although both the nadir hematocrit and blood transfusion were associated with mortality, acute kidney injury and length of stay, there was an additive risk when both anemia and transfusion occurred. Ranucci analyzed 16,154 cardiac surgery patients¹⁷ and found that major bleeding had an OR of 3.5 for 30 day mortality. In their model predicting mortality, preoperative anemia and transfusions had a multiplying effect.

So there is evidence that blood transfusion itself may be harmful. This has been the focus of recent research, leading to a variety of retrospective cohort analysis, and more recently, several randomized controlled trials.

An analysis of Jehovahs witnesses who had cardiac surgery between 1983 and 2011 in a single US centre⁶⁴ showed less operational bleeding and better 1 year survival for Jehovahs witnesses (N=332) than propensity matched non-Jehovas witnesses.

Koch et al. analyzed data on 11,963 patients from Cleveland Clinic Foundation 1995-2002⁶⁵ and showed that for every unit PRBC transfused during CABG surgery, there was an increased risk of mortality, renal failure, sepsis, cardiac complications and neurological event. This was followed by publication of long term data⁶⁶ showing that transfusion was associated with higher mortality rates up to 10 years post CABG surgery. The same group also demonstrated that transfusion during cardiac surgery was associated with reduced quality of life at 6 or 12 months post surgery⁶⁷.

Analysis of non-cardiac surgery data¹⁵ found the 30 day mortality for non-transfused patients, those receiving between 1 and 4 units PRBC and those with 5 or more PRBC units was 1.2%, 3.9% and 21.5% respectively.

Most transfusion data comes from retrospective analysis of cohorts. The obvious problem with these studies is the effect of confounding. For example it is likely that a cardiac surgeon will decline to operate on a Jehovahs witness patient who is at high risk of major bleeding during surgery. Patients who bleed more during surgery are more likely to be older and have co-morbidities such as cancer and renal impairment. These confounders are associated with poorer surgical outcomes. Furthermore, it is unclear whether bleeding itself may be the injurious process, rather than blood transfusion, because it is clear that patients who bleed more receive more units of PRBC.

There have been few randomized controlled trials which directly compared liberal blood transfusion strategies to restrictive ones. Carson et al. randomized 2016 patients at risk of cardiovascular disease who had undergone hip fracture surgery, to transfusion thresholds of either 100g/L or 80g/L⁶⁸. They

showed no difference in 60 day death or ability to walk across a room. The TRACS study⁶⁹ randomized 512 cardiac surgery patients to restrictive or liberal transfusion strategies. There was a nonsignificant difference in the combined end point of 30 day mortality and severe morbidity. A Cochrane review in 2012 combined a total of 19 trials⁷⁰, concluding that a restrictive transfusion strategy appears to reduce in-hospital death, but not 30 day mortality, severe morbidity or length of hospital stay.

Two RCTs have shed further light on the subject. Carson et al. recently published a study on 110 patients with acute coronary syndrome undergoing PCI⁷¹. In contrast to previous research, this showed significantly increased 30 day mortality in the restrictive group and a trend towards more MIs and unscheduled hospital admissions. In this case, it appeared that blood transfusion was a good intervention, which contradicts prior RCTs.

A Spanish study published last year randomized 921 patients presenting with severe upper gastrointestinal bleeding to restrictive or liberal transfusion strategies⁷². The study demonstrated not only reduced 6 week mortality with the restrictive strategy, but also fewer repeat bleeds, less requirement for rescue therapy and shorter hospital stays. The study is interesting because it is the first to recruit patients who are unambiguously bleeding (rather than on the basis of low hemoglobin levels), and argues strongly for a lesser role for blood transfusion.

The overall effect of this literature on daily physician practice is complex. My discussion with physicians has elucidated that some may approach upper GI bleeding with a more conservative transfusion strategy, however others, such as trauma physicians, pay little heed to this literature and believe strongly in the benefit of blood transfusion for injured and bleeding patients. Furthermore, it is difficult to imagine that blood transfusion would ever be with-held during massive hemorrhage, in instances when a patient may lose more than half of their blood volume. In particular, certain surgeries (such as cardiac, vascular and major orthopedic surgery) have a higher incidence of major bleeding, and I would predict that a large transfusion in these circumstances would be indicative of major blood loss.

The relevance to this project is that the practice of blood transfusion is, in general, changing, and the significance of a blood transfusion in relation to identifying patients who are bleeding may change in the future. Similarly, the practice of giving blood transfusion for anemia may also change and it is difficult to predict how a prescription of PRBC in The Ottawa Hospital will specifically identify a bleeding patient over an anemic patient.

Recent evidence suggests that blood transfusion may worsen patient outcomes. Physicians might change their transfusion prescribing practice in the future so we cannot rely on the presence of blood transfusion to identify clinically relevant bleeding.

Can we predict who will bleed?

Several recent cardiology papers have detailed models which help to predict which patients with acute coronary syndrome will bleed.

NSTEMI

⁵⁰Subherwal et al. derived and validated the CRUSADE prediction rule for in-hospital bleeding in 89,134 NSTEMI patient admissions. The CRUSADE prediction rule is a score from 0-100, split into quintiles, with a score >50 being very high risk of bleeding. Each successive quintile has a greater bleeding risk. The score was validated in Spain⁵¹ in a separate NSTEMI cohort and performed with a C-statistic of 0.72. The score uses 8 variables: hematocrit, creatinine clearance, heart rate, sex, signs of heart failure, blood pressure, vascular disease and diabetes.

STEMI

Several models have been published for STEMI patients, who are at the highest risk of bleeding. These include a Serbian model⁷³ that predicts 30 day bleeding (BARC type 3a or greater) post PCI for STEMI. Higher risk factors are female sex, creatinine clearance <60, history of peptic ulcer, Hb <125g/L and heart failure. Another analysis of the ExTRACT-TIMI 25 study¹³ found TIMI classified bleeding was associated with age, female sex, lower body weight and higher TIMI scores. The TIRTON-TIMI 38 study analysis¹² found independent predictors were age, female sex, ethnic origin, and antiplatelet drug type.

PCI

Rodriguez et al.⁷⁴ derived a model to predict bleeding in 453 patients who underwent emergency PCI. The independent predictors were age, STEMI, renal impairment and treatment with prasugrel. Ndrepepa et al.⁷⁵ showed that women were at higher risk of 30 day bleeding post PCI, especially access site bleeding. In a meta-analysis, Lin et al.⁷⁶ demonstrated that patients with BMI < 18.5 are at highest risk of postPCI bleeding, and that there is a reverse, J shaped curve where patients with the largest BMIs are also at a higher risk of post PCI bleeding.

Cardiac surgery

The Papworth score⁵³ was derived to predict postoperative bleeding in the first three hours after surgery. The score uses one point each for age > 75, BMI < 25, emergency surgery, aortic disease and surgery other than a single valve replacement or CABG.

Medical patients

Much less is known about predicting in-hospital bleeding amongst medical patients. There is no published model predicting the risk of in-hospital bleeding.

An RCT of 3746 intensive care patients⁷⁷ found a bleeding rate of 13.1% and a major bleeding rate of 5.6%. Predictors of bleeding were heparin therapy, antiplatelet therapy, prolonged APTT clotting tests, low platelet count, renal replacement therapy and surgery.

The risk of death from peptic ulcer bleeding is increased by the presence of cancer, liver disease and renal disease.²³

We know that warfarin for non-valvular atrial fibrillation increases the risk of bleeding events compared to aspirin alone,^{78;79} and that dual antiplatelet therapy increases the bleeding risk further.⁸⁰ A recent meta-analysis⁷ reported a crude 2.5% yearly risk of bleeding while taking warfarin for atrial fibrillation, and a 0.6% incidence of intracranial bleeding. There are several scoring systems for assessing the risk of bleeding in outpatients prescribed warfarin for stroke prophylaxis in atrial fibrillation. The HAS-BLED score⁸¹ determines bleeding risk based on age, prior bleeding history, therapeutic warfarin control, liver disease, renal disease, drug or alcohol abuse and prior stroke. The HEMORR2HAGES score⁸² was derived for use on large databases and includes predictive variables from other scoring systems: hypertension, age, alcohol use, liver disease, renal disease, prior bleeding history, stroke, falls risk, hemoglobin and platelet count. The ATRIA score⁸³ was derived on a larger administrative database containing 13,559 patients with non-valvular atrial fibrillation. The score uses similar variables and is more simple than the others: hemoglobin, renal function, age, prior bleeding and hypertension. Two recent prospective cohort studies^{84;85} found that all three scores had only moderate predictive ability with C-statistics between 0.5 and 0.6.

There are also scores derived to predict bleeding in patients treated with warfarin for venous thromboembolism. The RIETE score⁸⁶ uses almost identical variables: age, renal dysfunction, recent bleeding, cancer, hemoglobin and diagnosis of pulmonary embolism.

Bleeding scores are commonly integrated into outpatient clinical decision making for stroke prophylaxis, however there is no published study assessing the utility of any such score in hospitalized medical patients.

Studies have identified common patient characteristics which predict bleeding events. These characteristics might be useful in The Ottawa Hospital to identify those at risk, and to institute measures to mitigate bleeding events.

What can be done to mitigate bleeding?

Prospective audit

Cardiac surgery leads the way with bleeding safeguards. Perhaps because of the high risk nature of the surgery, performance indicators and reflective practice are the norm. In 2007, Wolfe et al.⁸⁷ published their experience in an Australian cardiac surgical unit, where the medical staff noticed there was an increase in the number of patients who underwent re-operation. The unit performed a formal audit which confirmed the suspicion, and prompted the group to review the contributing factors and implement change. This successfully reduced the rate of re-opening. More recently a similar paper was published from the US⁸⁸, where a cardiac unit was able to reduce the incidence of re-opening post CABG, by introducing a standard check list to be reviewed prior to chest closure in the operating room.

Medication prescription

Preoperative interventions

Anemic patients are at higher risk of postoperative bleeding and mortality^{17;61}. It is possible to increase the hemoglobin prior to surgery, if the anesthesiologist and surgeon work together to delay surgery and treat the anemia. Iron deficient patients can be prescribed an intensive course of iron.

For surgeries with high volume expected blood loss, patients can donate their own blood which is stored and re-infused when their blood is lost during surgery.

Intra-operative interventions

Epsilon aminocaproic acid and tranexamic acid are antifibrinolytic drugs that reduce bleeding in surgery. The serine protease inhibitor aprotinin has been used to reduce cardiac surgery bleeding, although is less used now because of safety concerns. Many hospitals use antifibrinolytic drugs routinely in major surgery.

During surgery it is possible to collect the blood lost from the surgical site in a sterile manner, to be immediately transfused back into the patient.

Anticoagulant prophylaxis

It is standard practice to provide venous thromboembolism prophylaxis during admission for major orthopedic surgery, as these patients are at significant risk of postoperative deep vein thrombosis or pulmonary embolism. There are several candidate anticoagulant drugs which have been studied for their efficacy in preventing venous thrombosis. Huisman et al.⁸⁹ performed meta-analyses of studies comparing dabigatran and enoxaparin, and rivaroxaban and enoxaparin, to establish the overall comparative efficacy and risk of bleeding. Enoxaparin had fewer episodes of venous thrombosis than dabigatran and a trend towards fewer bleeding events. Rivaroxaban had significantly fewer venous thrombosis but significantly more bleeding events. The two studies used different definitions of bleeding. Rivaroxaban comparative studies reported bleeding in 2-3% of patients and dabigatran reported bleeding in 5-6% of patients.

Yoshida et al.⁹⁰ compared the efficacy and safety of all available prophylactic anticoagulants in major orthopedic surgery including fondaparinux, bemiparin, apixaban, rivaroxaban and dabigatran against enoxaparin. The reported bleeding rates compared to enoxaparin varied, but apixaban appeared to be associated with the least bleeding. So keeping abreast of current evidence may provide guidance on the choice of prophylactic anticoagulant with the least risk of bleeding.

An analysis of 21,000 hospital encounters in the US⁹¹ found that properly applied hospital prophylaxis was associated with a lower bleeding rate compared to patients who had inadequate thrombosis prophylaxis.

Aspirin

Researchers have begun to look at other contributing factors in cardiac surgery bleeding. For example, an RCT compared the risks and benefits of giving a loading dose of aspirin the evening before surgery³⁵. They found an increase in postoperative bleeding in the group who had aspirin, however they also found a lower incidence of cardiovascular events long term, so it is not clear cut whether aspirin is overall a risk or a benefit. As yet there are no other prospective trials addressing this question.

A small cohort study³³ found patients taking aspirin had a higher incidence of postoperative hip surgery transfusion and a higher incidence death within a year.

Anti-inflammatory medications

Friedman et al.⁹² showed a nonsignificant increase in postoperative bleeding in patients receiving either dabigatran or enoxaparin for hip surgery prophylaxis, if they already took aspirin. Eriksson et al.⁹³ analyzed all studies comparing rivaroxaban to enoxaparin prophylaxis during hip surgery. They also showed that co-medication with a platelet function inhibitor (including an NSAID) was nonsignificantly associated with an increase in bleeding events.

Therapeutic anticoagulation

Warfarin is the traditional anticoagulation drug. Each patient requires a different dose of warfarin and it is difficult to predict the correct dose. Warfarin relies on a stable diet and can interact with other medications. As a result, warfarin dosing requires regular blood monitoring. There can be unpredictable swings in the effect of warfarin during acute medical illness, and when the warfarin effect is too great (supra-therapeutic), a patient is at risk of serious bleeding. Therefore, warfarin dosing and monitoring for acutely ill medical patients is an essential part of patient care.

Other anticoagulant medications, in particular dabigatran, is eliminated from the body by the kidneys. Acute changes in kidney function can have marked effect on the concentrations of dabigatran. Acute kidney injury is not uncommon in patients who are sick with other conditions, and if these patients take dabigatran anticoagulation, they are at risk of bleeding.

Most surgeries are too dangerous to perform on anticoagulated patients as the risk of major bleeding would be too high. It is routine practice to hold anticoagulant medications prior to performing surgery,

however this can put a patient at risk of thrombosis (such as stroke or deep vein thrombosis). In addition, each anticoagulant works in different ways and has a different half-life. Following surgery, many patients take a few days to return to their normal diet, and often remain at risk of bleeding for several days. Managing perioperative anticoagulant care can be a complex process and at The Ottawa Hospital, the Thrombosis clinic offers a service whereby Thrombosis physicians will supervise the process. So it is important that surgeons refer such patients to the Thrombosis service, to reduce the risk of perioperative bleeding.

Piazza et al.⁹⁴ analyzed 463 anticoagulation-associated adverse drug events. Of the 463, 59 were bleeding events. They determined that the root cause was a failure to recognize an underlying condition predisposing to bleeding in 58% and medication error in 40%. Medication errors can occur at several stages: the physician could prescribe the wrong dose, the nurse could mis-read the order (especially if hand written), and the nurse could give an incorrect dose to the right patient, or else the right dose to the wrong patient.

At first glance it seems that warfarin ordering should be straight forward, however there are many ways in which it can go wrong. Caudill-Slosberg et al.⁹⁵ published a detailed example of how mistakes can be introduced when using an electronic medical record and computerized physician order entry system. There is potential for error at every step in the care pathway.

Electronic surveillance

Given the high risk nature of anticoagulation medication, some hospital pharmacies have proactively introduced systematic electronic hospital surveillance. A hospital in the US⁹⁶ published their experience of introducing a real-time medicine safety dashboard, which highlighted supra-therapeutic warfarin and heparin levels, changes in creatinine levels and co-prescription of drugs with known interactions. It remains to be seen whether such electronic surveillance reduces medical error. A qualitative study in the Netherlands⁹⁷ interviewed physicians about when and why they turned off electronic alerts on the electronic medical record system. Their reasoning included seeing the alert many times, being familiar with the alert and their perception of the risk as low.

There are many opportunities where intervention in the patient care pathway could mitigate bleeding events. Such actions might include clinical team reflective practice with behavior modification, review of modifiable risk factors prior to surgery, active review of medication prescription pre and post surgery, and daily review of risk factors (medications, renal function and thrombosis prophylaxis) on medical wards. The optimal methods to conduct these interventions are as yet, not established.

Monitoring hospital bleeding events

We know that bleeding events occur in both medical and surgical patients, and that bleeding can lead to blood transfusion, longer hospital stays, kidney injury, MI and death. We also know that there are ways to predict which patients might bleed, and that we may be able to alter events by choosing surgical candidates carefully, choosing surgical techniques, carefully considering which drugs to prescribe and regularly evaluating the patient.

The Ottawa Hospital

The Ottawa Hospital has embarked on an ambitious commitment to transform the hospital into one of the safest in North America. The drive behind this mission comes from the The Ottawa Hospital data warehouse, where all electronic hospital data is chelated and stored. The 'ETrigger Project' has already successfully produced an effective unscheduled readmission alert, which feeds back to physicians via email when their patient is readmitted to the hospital within 30 days of discharge. This provides invaluable patient level data which until now, may have escaped the physician's attention. It provides an interface where the circumstances of the re-admission may be reviewed, and a basis for future improvements in patient management.

A hospital ETrigger for bleeding would be equally informative on several levels. At the most basic level, personal feedback to individual physicians about their patients' bleeding will promote a culture where bleeding is regarded as an adverse event. This in turn will raise the profile of bleeding and encourage physicians to review their daily practices. If errors have been made in patient care, a root cause analysis will aid development of new systems to avoid repetition of the same mistake. On a larger scale, an ETrigger would facilitate a monthly or yearly 'bleeding report'. The Ottawa Hospital does not record bleeding events currently, and there is no estimate of the frequency of bleeding or the burden this places on the hospital and patients. The report could function as an outcome measure, by which to evaluate the effectiveness of staff education, new system implementation and cultural behavior change. An effective, centralized monitoring system would accurately identify patients who were bleeding real-time. Ideally the system would be maximally specific (identifying true bleeding events) and sensitive (identifying all important bleeding events). It would function 24 hours a day, independent of manual chart review, and be cost effective.

A Bleeding ETrigger

We have seen that there is little prior research on bleeding and no unified definition. Most studies have used different ways of determining when a patient has bled, and there have been very few large database analyses of bleeding events. Developing a 'Bleeding ETrigger' for The Ottawa Hospital requires two processes. The first is to identify patients who are having bleeding events and when the bleeding events occur. The second is to identify elements archived within the hospital electronic database that could aid in remote identification of a bleeding patient.

In essence, building an ETrigger is a diagnostic study. We should have a gold standard definition to identify the bleeding events, and a list of potentially useful electronic indicators for bleeding events. At the outset of this study, neither element existed.

The Ottawa Hospital has committed to producing an electronic real-time trigger to identify patients who are bleeding on the wards. In this thesis I describe the process by which I developed a method and produced an electronic identifier for hospitalized bleeding patients.

STUDY AIM

The aim of this study is to derive a model to predict bleeding events in The Ottawa Hospital. This will be the foundation for The Ottawa Hospital bleeding ETrigger.

METHODS

At the outset of this study, the aim was to develop three separate electronic identifiers: one for perioperative bleeding, one for spontaneous bleeding and one for postoperative venous thrombosis. Following Stage 1 of the two stage project, there were four major modifications to the study methods.

1. It became apparent that there were considerable unforeseen complexities with identifying bleeding, and the project was re-aligned to develop an electronic trigger for bleeding events. Although the Stage 1 ground work for the postoperative venous thrombosis ETrigger was completed, an electronic identifier has not been developed.
2. The ETriggers project management decided to amalgamate the perioperative bleeding and spontaneous bleeding into a single bleeding ETrigger.
3. The ETriggers project management requested to restrict the electronic identifier to inpatient bleeding episodes (and not all bleeding events, as was the Stage 1 design)
4. The initial plan was to use the data warehouse electronic data in Stage 1 to identify potential electronic data elements that were associated with bleeding and thrombosis events. The manual chart read was performed to determine whether each patient was positive or negative for the event of interest, and all manually extracted data was collected as evidence for the presence or absence of the event. However after the completion of the chart read, the ETriggers project manager did not facilitate production of this electronic data, instead requesting that I use only the manually extracted data in the Stage 1 analysis.

The Ottawa Hospital data warehouse contains the electronic medical records for all encounters at the hospital. The warehouse is updated daily and archives all electronic information (pharmacy, laboratory, diagnostic imaging and physician reports).

The aim of this study was to identify a pool of electronic bleeding markers, and to test the performance of these markers when used together as a group, in an unselected patient population from The Ottawa Hospital.

This was essentially a diagnostic study where we identified the candidate electronic data elements, and documented when they were present and absent. In parallel to this, we documented whether each patient had a bleed and which patients did not have a bleed (our gold standard categorization). The diagnostic performance of those electronic data elements associated with the presence of a bleed were then assessed in an unselected group of inpatients.

There are several ways in which the candidate electronic markers could be identified.

The first option would be to take a previously derived bleeding definition (such as BARC or the ISTH definition) and translate the specific variables into electronic identifiers in the data warehouse. However BARC was derived to identify cardiac related bleeding only, and the ISTH definition depends on real time interaction with the admitting surgeon.

Other options included performing a Delphi study with hospital physicians, nurses, pharmacists and allied services, to identify perceived common associations with hospital bleeding events. This would produce an opinion driven identifier with the advantage that each specialty would have contributed their expertise. However there is little to suggest that hospital specialists can accurately identify bleeding patients or are aware of the risk factors for bleeding. It was possible that a Delphi study might have produced an identification method which performed poorly.

The ideal method would have been to follow a cohort of patients real time within the hospital. The cohort would be a cross section of all admitted patients, and each patient would be followed every day. This poses several problems. Firstly, the estimated bleeding rate is very low (likely less than 3% of all admitted patients), so the study would require many thousands of patients in order to identify relatively few bleeding events. Secondly, given the inefficient design, a much larger team of researchers would be required to actively follow so many patients.

We could modify the previous study design to follow several thousand unselected patients in retrospect through their data warehouse records. Although this reduces the workload since the cohort is now a retrospective cohort, each chart review would take between 5 minutes and 1 hour. We estimate that

the chart review would take 47 weeks, based on one researcher performing chart reviews 35 hours per week. Furthermore, this chart review would simply identify the electronic data elements associated with bleeding, and a second cohort review was required to assess performance of the candidate data elements.

Therefore the decision was taken to perform a retrospective chart review, to establish which elements of electronic data were candidate markers of bleeding. This had the advantage of reducing the sample size and increasing the number of bleeding events to analyze.

The study consisted of two parts,

STAGE 1: An exploratory retrospective cohort was identified from the data warehouse records, and each encounter was analyzed in detail by one researcher (KH). This facilitated production of an analytical database, which enabled identification of potential electronic identifiers of bleeding events at The Ottawa Hospital.

STAGE 2: A model derivation cohort was identified and the candidate prospective electronic identifiers were evaluated for their diagnostic utility.

Stage 1

Cohort building

A retrospective cohort of patients was identified from the hospital data warehouse. Patient encounters were selected on the basis of their International Classification of Disease, Canadian version 10 (ICD-10-CA).

A hand search of the ICD-10-CA codes, performed by KH, identified all bleeding and venous thrombosis codes (detailed in Appendix 1). The cohort was identified on the basis of these codes by a data warehouse analyst (NO).

Stage 1 was designed so that a quarter of the patients had an ICD-10 code for perioperative bleeding, a quarter coded for spontaneous bleeding, a quarter for postoperative venous thrombosis and a quarter had none of these codes.

The 4 predefined patient groups were identified as follows:

- 250 randomly selected inpatient encounters discharged between 1st October 2010 and 31st October 2011 with a surgery in the main operating room (hprcOperatingRoomNum = '01'). Each encounter also had to have a diagnostic code for bleeding (see Table 29, Appendix 1). The 31st October 2011 represented the latest date for which the data warehouse had discharge abstracts at the time of dataset creation (February 2012).
- 250 randomly selected inpatient encounters discharged between 1st October 2010 and 31st October 2011 with a surgery in the main operating room (hprcOperatingRoomNum = '01'). Each encounter also had to have a diagnostic code for venous thromboembolism (see Table 30, Appendix 1).
- 250 randomly selected inpatient encounters discharged between 1st October 2010 and 31st October 2011 with a diagnostic code for bleeding (see Table 9).
- 250 randomly selected inpatient encounters discharged between 1st October 2010 and 31st October 2011 that were not already selected for the above three groups.

During Stage 1 data extraction, it became apparent that there were many complexities to the analysis of bleeding, and the aim was realigned to develop electronic identifiers for bleeding only. The final analysis consisted of 'cases' (patient encounters with a bleeding event) and 'controls' (those encounters without a bleeding event, including encounters with postoperative venous thrombosis).

The reasoning behind selecting these populations was to identify patients who were likely to have experienced both perioperative and spontaneous bleeding, along with a cohort who were unlikely to have had a bleeding event. Therefore the cohort did not represent the real-life distribution of these events. We did not rely on the ICD-10 coding to determine whether each patient had had a bleeding event. Instead, this was determined by the manual chart read.

Chart data extraction

A single researcher (KH) spent over 200 hours reading through the charts for each identified encounter. The researcher is a physician (a Thrombosis Fellow) with contemporary clinical experience of managing patients who have a bleeding event in The Ottawa Hospital.

The aim of this data extraction process was to

1. Determine whether the patient had had a bleeding event (blinded to the ICD-10 coding)
2. Classify the bleeding event as perioperative/spontaneous, inpatient/outpatient, and by bleeding site
3. Collect data on potential electronic identifiers of bleeding patients

Although the encounters were selected on the basis of their ICD coding, the researcher was blind to this coding and the patients were ultimately classified as 'bleeding event negative' and 'bleeding event positive' on the basis of the data extracted from the chart read only.

The charts were read systematically in the following order:

Operation reports

Hemoglobin reports

PRCB transfusion prescriptions

Hand written daily physician and nurse charts

CT scan, MR scans and ultrasound scan results

Thrombosis clinic letters

Admission dates

Anticoagulant and antiplatelet medications

Endoscopy reports

(All of the above were read in all patient encounters.)

Data point definitions

For **all surgical patients**, the following information was extracted from the notes

Specialty: the admitting specialty at the time of the bleeding event

Surgery: type of surgery

Hemoglobin drop: the drop between preoperative hemoglobin (taken within 60 days of surgery) and postoperative hemoglobin (taken within 7 days of surgery).

Transfusion: number of PRBC units transfused between the start of surgery and 7 days later.

Calculated hemoglobin drop: hemoglobin drop + (number of units PRBC x 10)

Cancer: patient currently receiving active or palliative cancer treatment

Written physician documentation of bleed: a physician had documented that a bleeding event took place

Imaging confirmation of bleed: a CT, MRI or ultrasound report stated that there was a bleed

Surgery for bleed: patient required to have a second operative procedure to control bleeding at some point between skin closure for initial surgery and 14 days later.

Endoscopic confirmation of bleed: an endoscopy report recorded that there was bleeding from the GI tract

Tamponade: the patient developed pericardial tamponade as a result of bleeding into the pericardial space

Readmission: the patient was readmitted for treatment of their bleeding, within 30 days of surgery

Death from bleeding: cause of death was bleeding, as indicated in medical chart, death certificate or autopsy

Antiplatelet medication: a record of antiplatelet medications prescribed on the days preceding the bleed, the day of the bleed and following the bleed

Anticoagulant medication: a record of anticoagulant medications prescribed on the days preceding the bleed, the day of the bleed and following the bleed

Time to bleed: number of days between surgery and the bleeding event

Deep vein thrombosis: the patient was diagnosed with deep vein thrombosis during admission

Pulmonary embolism: the patient was diagnosed with pulmonary embolism during admission

Postoperative thrombosis: the patient was diagnosed with deep vein thrombosis, pulmonary embolism or both within 42 days of surgery

Bleeding site: the anatomical site of bleeding

Non-surgical patients

Specialty: the admitting specialty

Cancer: patient currently receiving active or palliative cancer treatment

Spontaneous bleed: whether a bleeding event had occurred or not

The following data was recorded for **non-surgical patients who had a bleeding event**

Hemoglobin drop: the drop in hemoglobin occurring after the bleeding event

Transfusion: number of PRBC units transfused within 7 days of bleed

Calculated hemoglobin drop: hemoglobin drop + (number of units PRBC x 10)

Written physician documentation of bleed: a physician had documented that a bleeding event took place

Imaging confirmation of bleed: a CT, MRI or ultrasound report stated that there was a bleed

Surgery for bleed: patient required to have an operative intervention for their bleed

Endoscopic confirmation of bleed: An endoscopy report recorded that there was bleeding from the GI tract.

Tamponade: The patient developed pericardial tamponade as a result of bleeding into the pericardial space

Readmission: The patient was readmitted for treatment of their bleeding within 30 days of a previous admission

Death from bleeding: Cause of death was bleeding, as indicated in chart, death certificate or autopsy.

Antiplatelet medication: All antiplatelet medications prescribed prior to or on the day of the bleed.

Anticoagulant medication: All anticoagulant medications prescribed prior to or on the day of the bleed.

Bleeding site: The anatomical site of bleeding

In the case of duplicate patient presentations, the encounter was analyzed only once, with all outcomes recorded. When the researcher (KH) was unclear how to classify a variable, the encounter was reviewed with the thesis supervisor (AF).

Determining the gold standard definition of bleeding

It became apparent from an early stage that it can be difficult to classify a bleeding event. For example, if a patient is documented to have had hematuria for an hour after urethral catheterization, does this qualify as significant bleeding? In particular, it appeared from the calculated hemoglobin drop that many surgical patients had lost significant volumes of blood, however this was seldom ever documented in the chart.

No previously reported bleeding definition could be applied (see Tables 7 and 8) because this is a retrospective cohort and we were unable to ask the opinion of each surgeon in real-time (as per the ISTH definition, Table 8). Furthermore, the ISTH criteria define major bleeding, but not relevant minor bleeding, (which this study aims to capture). We could not apply the cardiology criteria since cardiology patients made up the minority of the exploratory cohort.

A panel was convened, consisting of a Thrombosis and bleeding expert (PW), an Internal Medicine and data warehouse expert (AF) and the author (KH). A consensus definition of bleeding was established after review of bleeding definitions and Stage 1 data.

The Definition of Bleeding

Bleeding that fulfills the following criteria:

Is documented by the physician or surgeon in the chart, OR

Is documented by imaging, OR

Is documented by endoscopy

AND

Necessitates an intervention such as surgery, transfusion, holding anticoagulant or antiplatelet medications, prolongs hospital admission, or leads to readmission to hospital.

Case cohort dataset analysis

The demographics of the cohort were described in terms of specialty, surgery type and evidence of bleeding event. Patient encounters were classified according to the bleeding definition. Spontaneous bleeding was further divided into in-hospital spontaneous bleeding and spontaneous bleeding that started at home.

The dataset was analyzed by patient encounters that were 'bleeding event positive' and those that were 'bleeding event negative'. The diagnostic utility of number of PRBC transfused, hemoglobin drop and calculated hemoglobin drop were compared using the shape of the receiver operating characteristic (ROC) curve, and the area under the curve. Separate analyses were performed for the detection of perioperative bleeding, all in-hospital bleeding and all bleeding.

The diagnostic utility of antiplatelet medication prescription, anticoagulant medication and cancer were assessed by comparing proportions of patients in each group who were positive for the variable.

The dataset was collected in Microsoft Access and exported into SAS version 9.3 for analysis. Plots and graphs were produced in IBM SPSS statistics version 21.

Defining candidate variables to identify bleeding

The analysis was performed by KH and reviewed with AF.

The choice of candidate electronic identifying variables was influenced by several factors:

1. A clear diagnostic association between the variable and bleeding events (as measured by the area under the ROC curve > 0.5).
2. The most prevalent types of bleeding and their specific electronic identifiers
3. The ease of capture of the electronic data
4. The availability of pre-existing, validated electronic triggers

Stage 2

A decision was made to limit the model derivation dataset to those patients who were given a blood transfusion. This had the advantage of identifying a single bleeding event per encounter (unlike in the exploratory set where several patient encounters included more than one bleeding event), and provided a specific date to scrutinize for each encounter (rather than examining the whole encounter which, on occasion, lasted over a year in length). Furthermore, there was the expectation that it would increase both the prevalence of bleeding and the derived electronic identifier specificity precision.

Model derivation set creation and sampling

A model derivation dataset was produced by a data warehouse analyst (JT). The dataset consisted of encounters discharged between the 1st November 2011 and the 28th February 2013 (the most recent health record abstracts available). Each encounter had to have had at least one transfusion occurring after 1st April 2011. This was to capture all patients who had been transfused, even if they had been admitted up to six months previously. The first transfusion was used as the trigger event and only one trigger event per encounter was analyzed.

The data warehouse analyst (JT) developed a method to identify all the candidate variables within the data warehouse archives, and their presence or absence for each transfusion episode was recorded in the dataset.

From this complete dataset, a random sample of 12% was identified, for chart review and further data extraction. This was the maximum number of charts that the author could read in the time limits of her fellowship, which ended in August 2013. The single reviewer (KH) spent 120 hours reading the charts for each patient encounter, for data extraction.

The aim of this data extraction and analysis process was to

1. Determine whether a bleeding event had occurred using our definition
2. Determine whether each candidate variable was present or absent (blinded to the analyst's data)
3. Establish the accuracy of electronic variable identification within the data warehouse archives
4. Establish a model to identify bleeding events

Data point definitions for the model derivation cohort

The following data were extracted from all dataset encounters

Specialty: admitting specialty at time of the transfusion

Operation: operation type if an operation occurred prior to the transfusion

Bleed: bleeding event occurred or not at the time of the transfusion

Type of bleed: perioperative bleed, spontaneous bleed, postpartum bleed

Bleeding site: anatomical site of the bleed

Number of PRBC: number of units of PRBC transfused within the first 24 hours

Endoscopy: the patient had an endoscopy within -24 and +24 hours after the transfusion, regardless of endoscopy findings

Readmission: the patient was readmitted within 30 days of a prior admission

Antiplatelet and anticoagulant medication: the patient was prescribed both antiplatelet and anticoagulant medications (according to the electronic medical records) on the day of their bleeding event

Antiplatelet and anticoagulant medication during encounter: the patient was prescribed both antiplatelet and anticoagulant medications (according to the electronic medical records) concomitantly at some point during this encounter

Return to the operating room: the patient had a second operation within -24 and +72 hours of their transfusion, having had an index operation within the last 7 days

Following chart review and data extraction, the results of all candidate variables were compared to the data analyst identified candidate variable results. All discrepant results were reassessed by the author (KH) in order to

1. double check what actually occurred
2. determine reasons why an electronic search may not have produced the same result

Analysis

1. A descriptive analysis of the cohort demographics was performed.
2. Candidate variables were assessed with univariate logistic regression analysis. Those with significant associations with bleeding were entered into a multiple logistic regression analysis using conditional modeling with forward selection. The C-statistic was calculated. The optimal cut point probability threshold to determine bleeding was assessed by comparing sensitivities and specificities of the cut points.
3. The sensitivity and specificity of the electronic identification of the model variables was assessed, and reasons for false positives and false negatives were explored.
4. An analysis of the exploratory cohort information was performed to describe the bleeding events in patients who had not been transfused, since these events were not represented in the model derivation cohort.

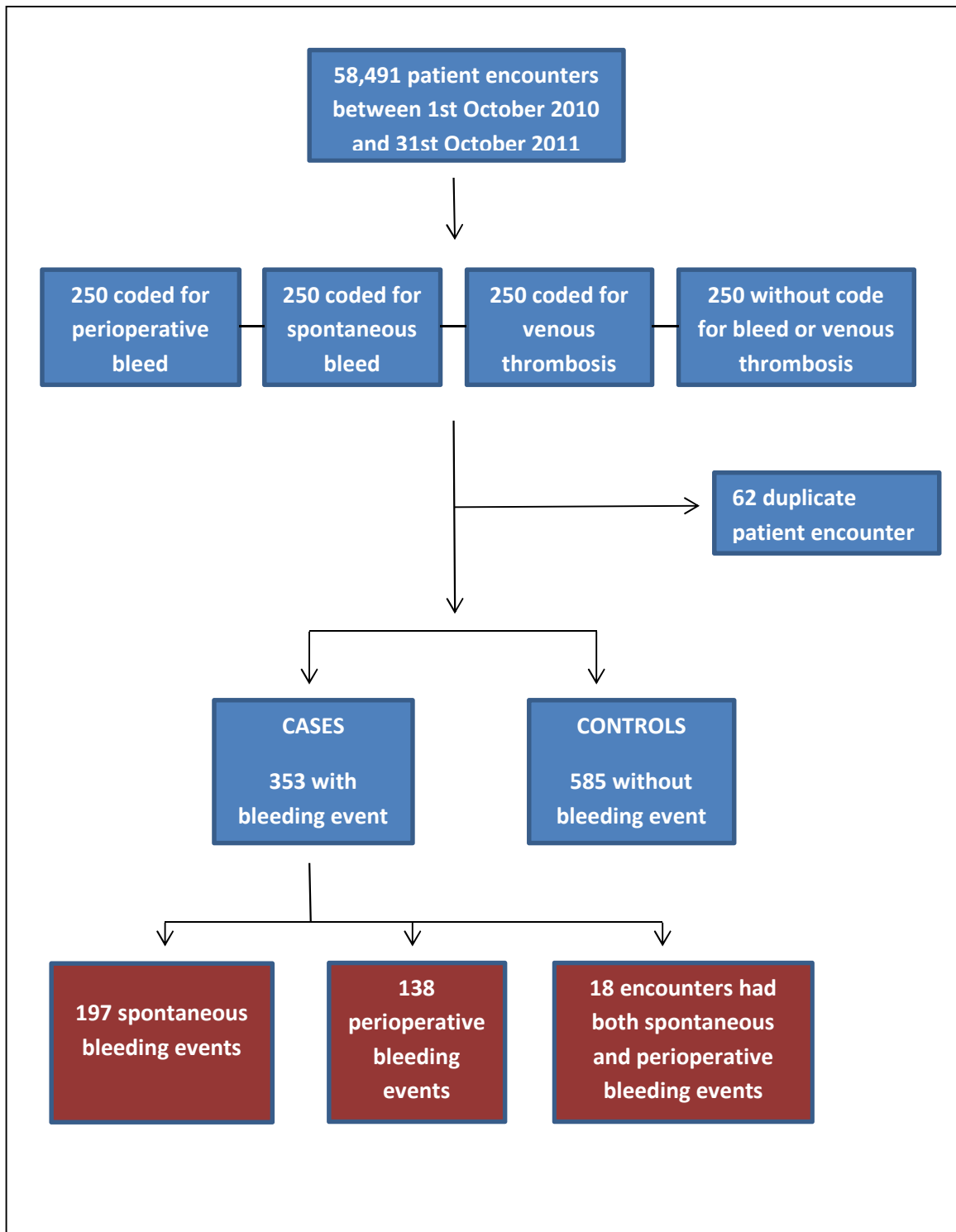
During the model building stage, the candidate variables were defined by the results of the chart review only.

As before, the data was collected in Microsoft Access and exported into SAS version 9.3 for analysis. Plots and graphs were produced in IBM SPSS statistics version 21. 95% confidence intervals for proportions were calculated using the Exact method.

RESULTS

Exploratory cohort

Figure 1: Flowchart for the retrospective exploratory dataset



Appendix 2 breaks down the cohort by admitting specialty, and describes the type of surgeries performed during the encounter. The largest group of patients was medical inpatients (20%) comprising internal medicine and all of the medical specialties, including oncology and radiation oncology. Some of these patients had undergone surgery but were admitted under medicine at the time of their bleeding event. Although most patients admitted under surgery had an operation, not all required surgery. In addition, some patient admitted under one surgical specialty had undergone surgery with a different specialty.

Table 9: Characteristics of exploratory cohort	
	Number
Men	474/938 (50.8%)
Adults	911/938 (97.1%)
Neonates	27/938 (2.9%)
Age	Median 63 (IQR 48-76)
Cancer	185/938 (19.7%)
Trauma patients	26/938 (2.8%)
Postoperative venous thrombosis	128/657 (19.5%) of operative patients
Elixhauser co-morbidity index	Median 0 (IQR 0-6)

A few neonates were identified in the cohort. The Ottawa Hospital has an obstetric and neonatal unit, although it does not admit children. A fifth of the cohort had cancer and a fifth of the surgical patients were diagnosed with venous thrombosis. Cancer, bleeding and venous thrombosis are frequently seen together as cancer is a risk factor for both.

Table 10 shows the descriptive bleeding outcomes in 657 patients who had surgery. We have no hemoglobin results for 60 surgical patients as they did not have either a pre- or postoperative blood count. We could make an assumption that, since their admitting surgeon did not request the test, it is unlikely that they lost a lot of blood during surgery. Most patients who bled had more than one positive finding, for example bleeding was recorded by the admitting doctor and again on endoscopy.

Table 10: Bleeding variables for perioperative patients N=657			
Variable	Encounters with result	Median	IQR
Hemoglobin postoperative drop	597/657	27 g/L	16-41 g/L
Red cell transfusion	657/657	0 units	0-1 unit
*Calculated hemoglobin drop	597/657	33 g/L	19-58 g/L
Time (days) to bleed after surgery	657/657	2	2-3
		Number positive	% of operative patients
Written physician documentation of bleed	657/657	144	21.9
Imaging confirmation of bleed	657/657	36	5.5
Hemorrhagic cardiac tamponade	657/657	6	0.9
Return to operating room for bleed	657/657	68	10.4
Readmission for bleed	657/657	16	2.4
Endoscopic confirmation of bleed	657/657	19	2.9
Death from bleeding	657/657	10	1.5
Perioperative bleed after 7 days	657/657	25	3.8
*Calculated hemoglobin drop = (drop in hemoglobin (g/L) between pre and 7 days postoperatively) + (number of units red cell transfusion x 10)			

In Figures 2 to 4, we compare surrogate measures of blood loss by different surgical procedures. Outliers are represented by the ^o symbol and outliers which are more than 3 times the value of the 75th percentile are represented by *. Within this cohort, cardiac bypass and valve surgery, along with prostatectomies, seem to have the largest calculated blood loss, however the drops in hemoglobin are not vastly different in these surgeries, compared with other types. In fact, some general surgery encounters have the greatest drops in hemoglobin, which shows that different surgeons may have different transfusion thresholds. Since this is a select population, we cannot extrapolate the findings to the general in-hospital patient population.

Figure 2: Distribution of the calculated hemoglobin drop by type of surgery

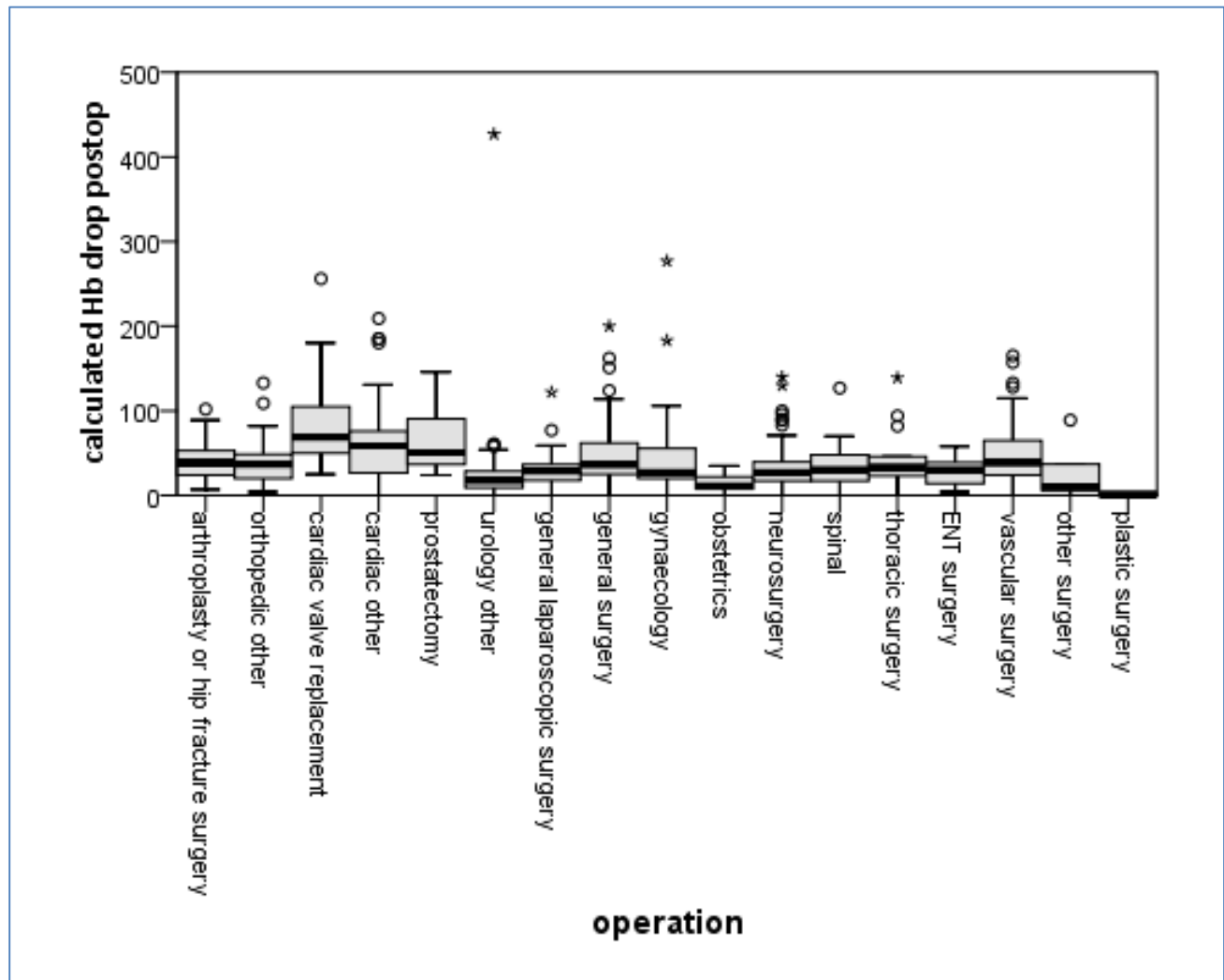


Figure 3: Distribution of number of PRBC units per patient, by type of surgery

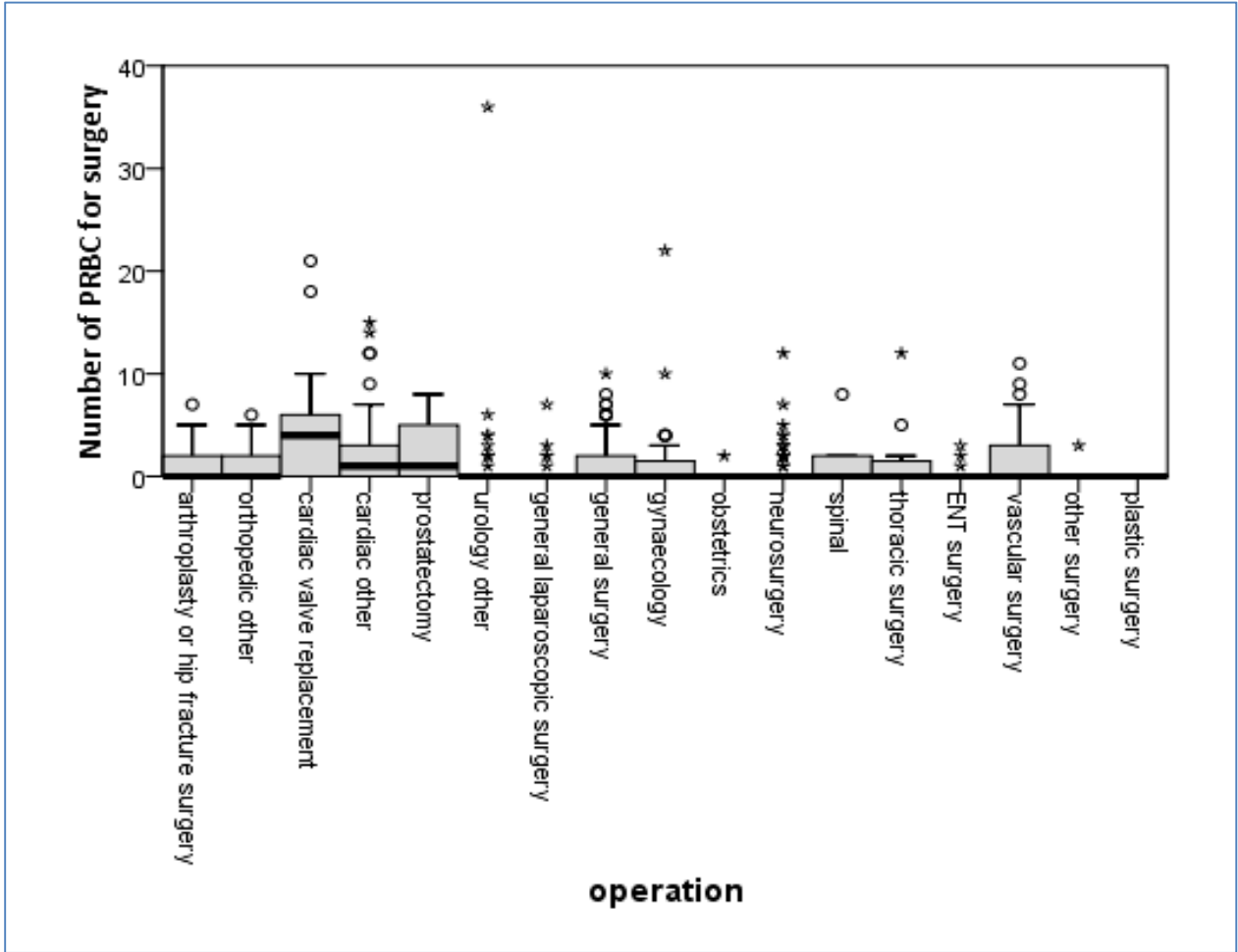


Figure 4: Distribution of drop in hemoglobin results by type of surgery

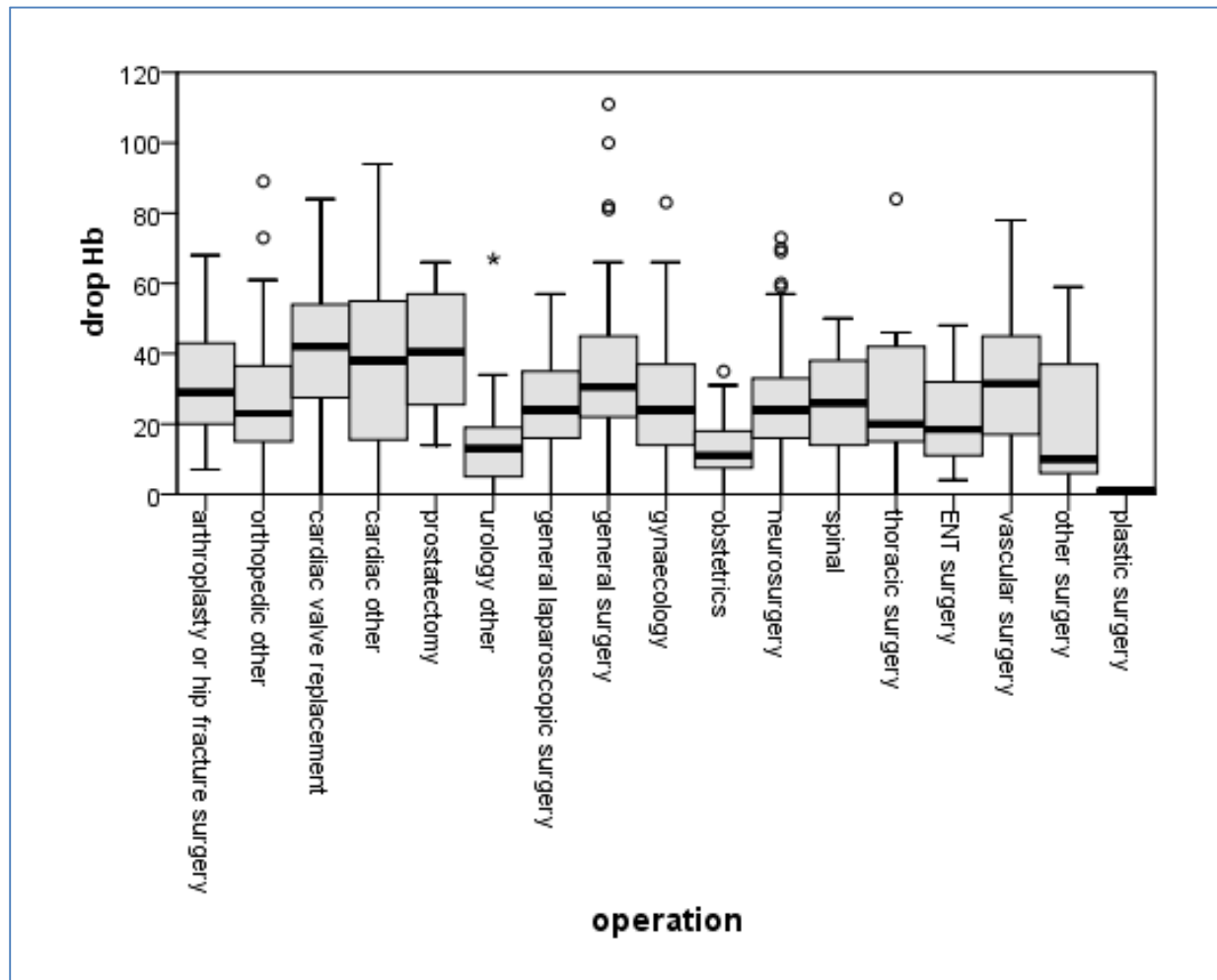


Table 11 shows the descriptive bleeding outcomes in 281 patients who did not have surgery. Details of hemoglobin and transfusions were collected only for those who had a bleeding event. The median calculated hemoglobin drop is similar to that seen with the operative patients.

Table 11: Bleeding variables for non-operative patients N=281			
Variable	Encounters with result	median	IQR
*Hemoglobin drop	85/281	20 g/L	6-35 g/L
*Red cell transfusion	85/281	0 units	0-0 unit
**Calculated hemoglobin drop	85/281	35 g/L	13-60 g/L
		Number positive	% of non-operative patients
Written physician documentation of bleed	281/281	102	36.3
Imaging confirmation of bleed	281/281	36	12.8
Surgery for bleed	281/281	14	5.0
Endoscopic confirmation of bleed	281/281	39	13.9
Death from bleeding	281/281	14	5.0
*Hemoglobin and transfusion data only collected on patients with bleed			
**Calculated hemoglobin drop = (largest drop in hemoglobin (g/L) between pre and 7 days postoperatively) + (number of units red cell transfusion x 10)			

Table 12 summarizes the bleeding events, as defined by our agreed definition of bleeding. There was a large proportion (70%) of spontaneous bleeding among the 281 non-surgical patients. A perioperative bleeding event occurred in 21% of the surgical cohort patients.

Table 12: Description of bleeding events in exploratory cohort		
		Number (%) Total N=938
*Bleeding events		353 (37.6)
	No bleed	585 (62.4)
	Spontaneous bleed	197 (21.0)
	Perioperative bleed	138 (14.7)
	Perioperative and spontaneous bleed	18 (1.9)
	Postpartum bleed	0 (0.0)
*Bleeding sites		**371 total
	Operation site	123 (13.1)
	Intracranial	91 (9.7)
	Gastrointestinal tract	79 (8.4)
	Hematuria	21 (2.2)
	Hematoma, intra-abdominal or pelvic	9 (1.0)
	Vaginal	7 (0.7)
	Retroperitoneal	7 (0.7)
	Aortic dissection	5 (0.5)
	Epistaxis	5 (0.5)
	Hemothorax	5 (0.5)
	Hemopericardium	4 (0.4)
	Hemoptysis	4 (0.4)
	Hematoma, skin	4 (0.4)
	Hematoma, muscular	3 (0.3)
	Ruptured ectopic pregnancy	1 (0.1)
	Site undetermined	1 (0.1)
	Leaking aortic aneurysm	1 (0.1)
	Adrenal	1 (0.1)
*Exploratory cohort therefore bleeding rates not reflective of hospital population incident rates		
**18 patients had both a spontaneous bleed and a perioperative bleed, 353 patients had bleed event		

The distribution of bleeding sites differed between perioperative and spontaneous bleeds (see Appendix 3). Patients who underwent cardiac catheterization were included in the 'operative' group for the purposes of this comparison. The majority of perioperative bleeds were from the surgical bed. In comparison, the majority of spontaneous bleeds were from the GI tract or intracranial bleeds. Most intracranial bleeds and ruptured aortic aneurysms occurred in outpatients. Most inpatient spontaneous bleeds were from the GI tract.

Table 13 shows the distribution of candidate markers of bleeding, between the patient groups. Although it is important for a bleeding trigger to identify all bleeding events, it seems that it would be most useful to identify those which start in the hospital, since these are the events we can act to avert. Bleeding sites differed between bleeds starting in-hospital and those starting at home (Appendix 3). Therefore it is possible that identifiers of in-hospital bleeding may differ from those for bleeding events which start at home. Our transfusion data is limited by the lack of information on patients who did not have surgery and did not bleed. However, 55% of patients who bled were given a blood transfusion, compared to 22% of surgical patients who did not bleed. 69% of in hospital bleeding events received a blood transfusion. When we compare the proportion of patients taking antiplatelet and/or anticoagulant medication, we find that there is little difference between those who don't bleed and those who do. However, if we compare those who have an 'in-hospital bleed' (a bleed that started in the hospital) to those who don't bleed, we find that in general, more people who have an 'in-hospital bleed' are taking these medications.

Table 13: Analysis of potential clinical bleeding predictors							
	No bleed N=585	Perioperative bleed N=138	Spontaneous bleed N=197	Perioperative and spontaneous bleed N=18	All bleeds N=353	All inpatient bleeds N=182**	Total N=938
PRBC transfusion	*109/501 (21.8%) who had surgery	99 (75.0%)	85 (43.1%)	9 (50.0%)	193 (54.7%)	124 (68.9%)	N/A
Median (IQR) number of PRBC units	*0 (0-1) who had surgery	2 (0-6)	0 (0-2)	0 (0-5)	1 (0-3)	2 (0-5)	N/A
1-3 units PRBC	*81/501 (16.2%)	50 (36.2%)	56 (28.4%)	3 (16.7%)	109 (30.9%)	62 (34.1%)	N/A
4 or 5 units PRBC	*23/501 (4.6%)	14 (10.1%)	18 (9.1%)	3 (16.7%)	35 (9.9%)	21 (11.5%)	N/A
6 or more units PRBC	*5/501 (1.0%)	35 (25.4%)	11 (5.6%)	3 (16.7%)	49 (13.9%)	41 (22.5%)	N/A
Cancer	118 (20.2%)	35 (25.3%)	39 (18.8%)	3 (33.3%)	77 (21.8%)	42 (23.1%)	185 (19.7%)
Antiplatelet	178 (30.4%)	68 (49.3%)	19 (9.6%)	5 (27.8%)	92 (26.1%)	75 (41.2%)	270 (28.8%)
Prophylactic dose anticoagulant	316 (54.0%)	91 (65.9%)	57 (28.9%)	9 (50.0%)	157 (44.5%)	106 (58.2%)	473 (50.4%)
Full dose anticoagulant	66 (11.3%)	20 (14.5%)	3 (15.2%)	1 (5.6%)	24 (6.8%)	21 (11.5%)	90 (9.6%)
Antiplatelet and anticoagulant	146 (27.4%)	68 (49.3%)	15 (7.6%)	5 (27.8%)	88 (24.9%)	75 (41.2%)	235 (25.1%)
* Denominator is all surgical patients who did not have a bleed. No data for non-surgical patients who did not have a bleed. **3 patients with spontaneous inpatient bleed also had perioperative bleed, 26 had spontaneous inpatient bleeds, 138 had postoperative bleeds and 15 had spontaneous bleed at home and perioperative bleed. N/A = not applicable, total unknown							

Figure 5: Comparison of surrogate measurements of blood loss in identifying perioperative bleeding

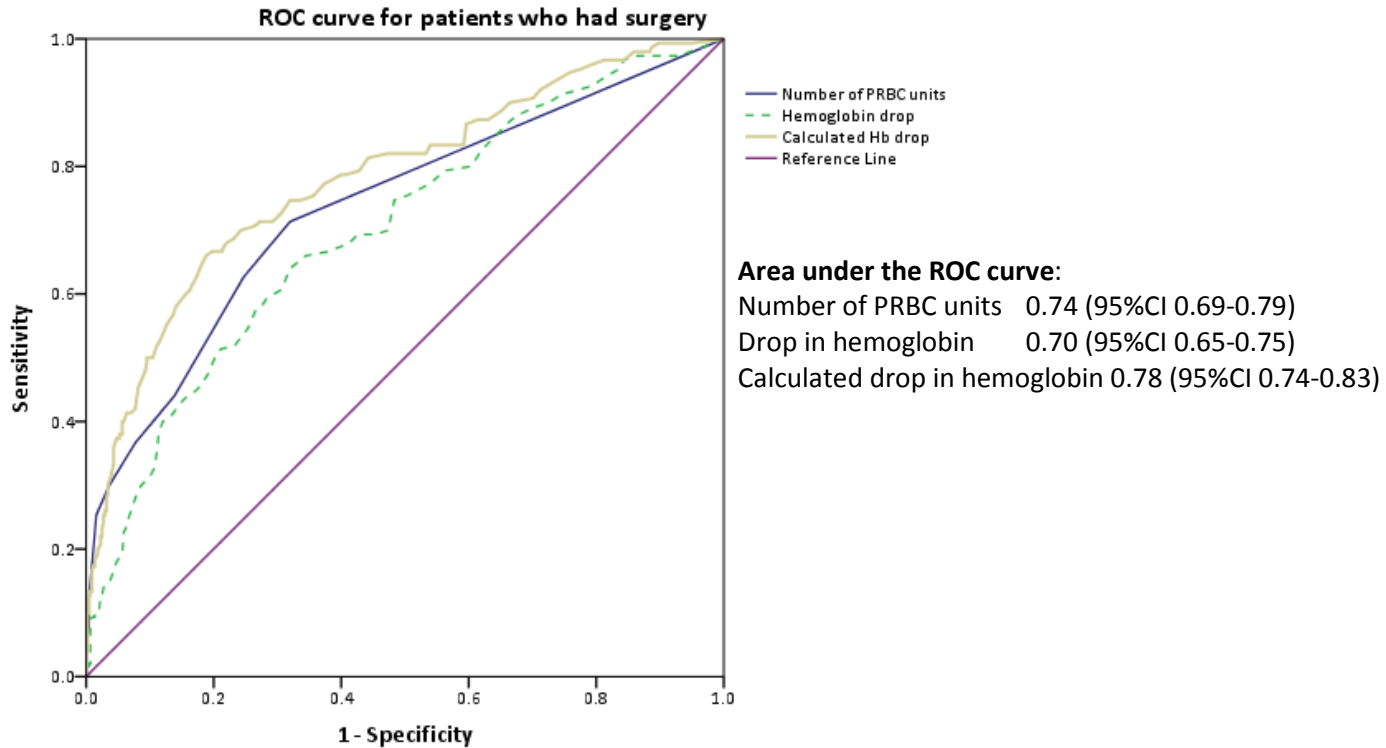


Figure 6: Comparison of surrogate measurements of blood loss in identifying in-hospital bleeding

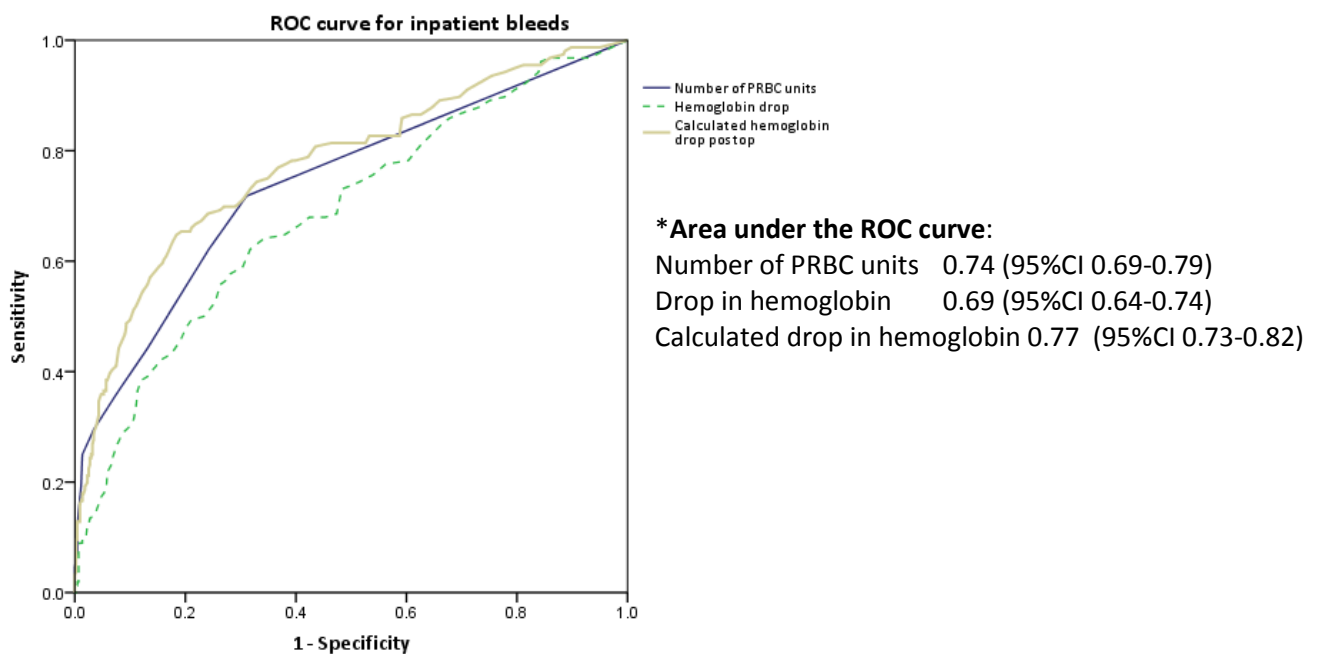
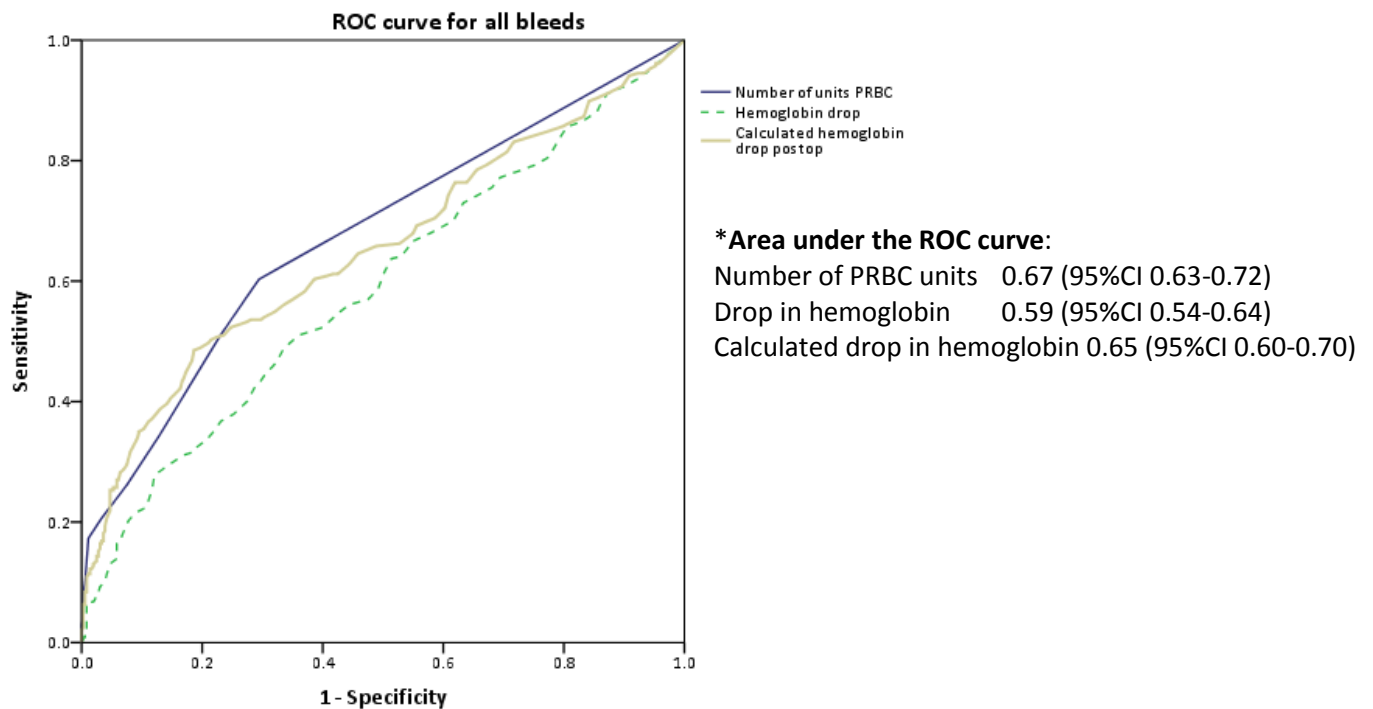


Figure 7: Comparison of surrogate measurements of blood loss in identifying all bleeding



* There are no transfusion or hemoglobin data for nonsurgical patients who did not have a bleed

Figures 4 to 6 compare the areas under the ROC curves for the three methods of measuring blood loss: number of PRBC transfusions, drop in hemoglobin and the calculated drop in hemoglobin. There is a trend towards the drop in hemoglobin being less discriminant between groups than the other two options, although the three indicators perform similarly.

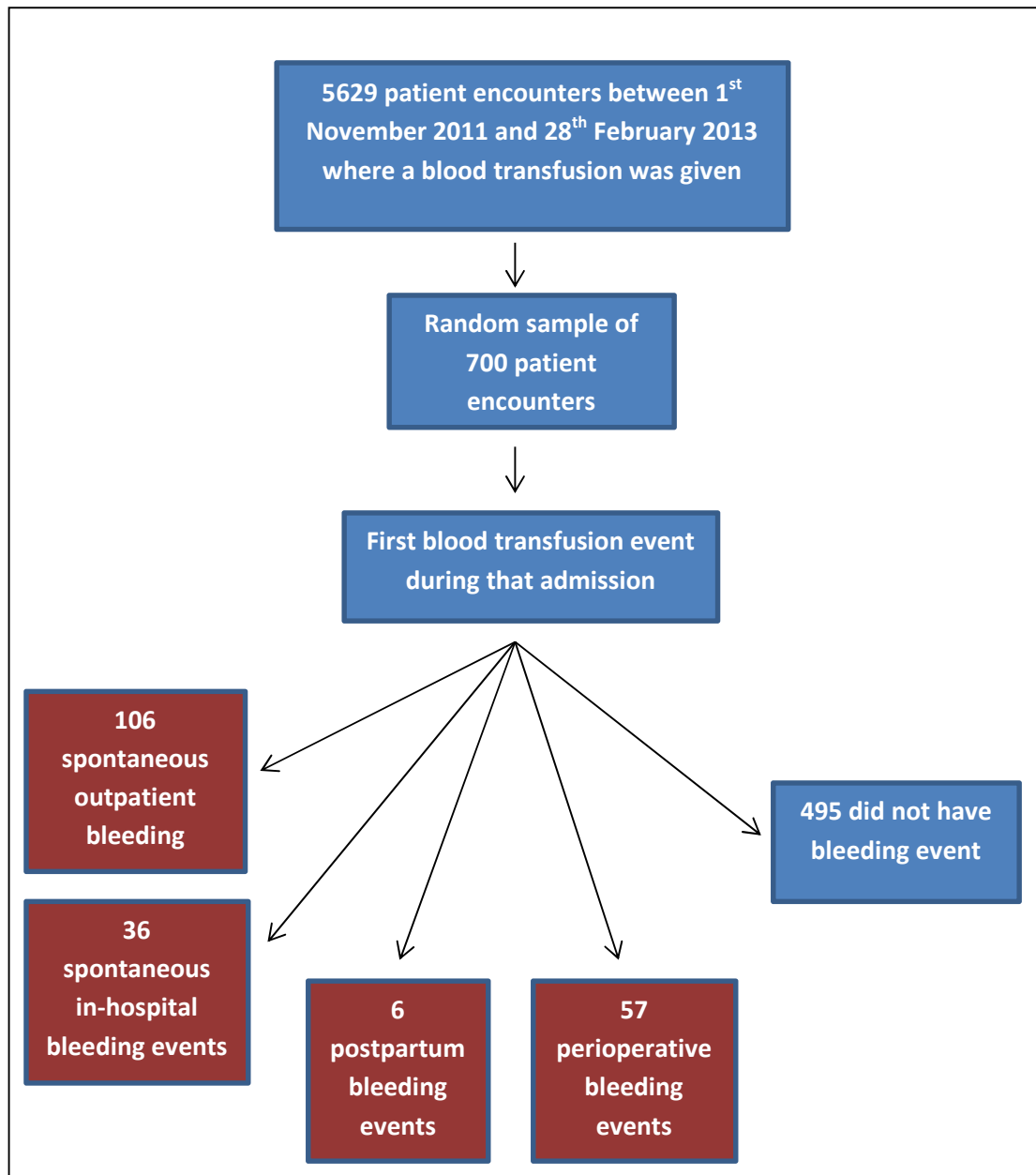
The chosen candidate variables for inclusion into an electronic identifier for bleeding are detailed in Table 14.

Table 14: Chosen bleeding identifiers to evaluate in model derivation set		
Variable	Details	Reasoning
*Number of units PRBC	Categorized into '0', '1-3', '4 or 5', and '6 or more'	More easily measured electronically than Hb drop or calculated Hb drop. ROC area under curve shows significant association.
**An endoscopy procedure	Positive or negative	21% of all bleeding events were from the GI tract.
**Re-operation within 7 days of initial surgery	Positive or negative	44% of perioperative bleeds required repeat surgery.
*Co-prescription of an anticoagulant and antiplatelet medication	Positive or negative	Co-prescription was more prevalent amongst encounters with in-hospital bleeding. Clinical logic that suggests the medications should increase bleeding.
**Unplanned re-admission to hospital within 30 days of discharge	Positive or negative	Easily measured as the data warehouse has already produced an electronic identifier for this variable. No data to support its use for bleeding, however simple to assess in model derivation set.
*Exploratory cohort data from all surgical patient encounters, and those with spontaneous bleeding. No data on encounters without surgery or spontaneous bleeding **Exploratory cohort data limited to those with bleeding events. No data on patient encounters without bleeding event		

Model derivation cohort

In total, there were 5629 patient encounters discharged between the 1st November 2011 and the 28th February 2013 with a transfusion occurring after 1st April 2011. A random sample of 700 (12.4%) were identified for chart review by KH (see Figure 8).

Figure 8: Flow chart for model derivation dataset



The median age of the 700 patients in the model derivation set was 69 (IQR 58-79). Fifty percent (350 patients) were male. The median Elixhauser co-morbidity score was 4 (IQR 0-11). Table 15 shows the distribution of bleeding events among the 700 encounters. The most prevalent site was bleeding from the GI tract, followed by surgical bed bleeding. Unlike the exploratory cohort, the sample came from all patients who were transfused and therefore the prevalences represent those in this hospital population.

Table 15: Description of bleeding events in the model derivation cohort		
		Number (%) Total N=700
Bleeding events		205 (29.3)
	Perioperative bleed	57 (8.1)
	Spontaneous bleed	142 (20.3)
	Postpartum bleed	6 (0.9)
Bleeding sites	Gastrointestinal tract	78 (11.1)
	Operation site	50 (7.1)
	Hematuria	15 (2.1)
	Vaginal	10 (1.4)
	Hematoma, skin	8 (1.1)
	Hematoma, muscular	9 (1.3)
	Hematoma, intra-abdominal or pelvic	8 (1.1)
	Postpartum bleed	6 (0.9)
	Epistaxis	5 (0.7)
	Hemoptysis	3 (0.4)
	Intracranial	3 (0.4)
	Retroperitoneal	2 (0.3)
	Hemothorax	2 (0.3)
	Ruptured ectopic pregnancy	2 (0.3)
	Intraperitoneal	1 (0.1)
	Multiple sites	1 (0.1)
	Hemopericardium	1 (0.1)
	Leaking aortic aneurysm	1 (0.1)

Comparison of bleeding location is detailed in Appendix 4. Again we found that surgical bed bleeding was the most common peri-procedural bleeding and GI tract bleeding, the most common type of spontaneous bleeding. Three quarters of GI bleeding requiring transfusion, starts in the home.

Medicine had the greatest number of encounters where a blood transfusion was given, followed by cardiac surgery. Details of bleeding events by surgery type are given in Appendix 5. In order to analyze the incidence of bleeding in relation to admitting specialty and type of surgery, an analysis was performed to identify whether certain specialties or surgeries were particularly high risk (Table 16).

In this sample of hospitalized patients who were transfused, the high risk specialties for bleeding events were trauma and obstetrics. The intermediate-high risk specialties were medicine, cardiology and gynecology. In the model derivation dataset, medical and radiation oncology were classified separately under the term 'oncology', and hematology was given a separate classification from all other medical specialties. Being transfused in either hematology or oncology was much less likely to represent a bleeding event.

Each specialty was allocated either low, intermediate or high risk of bleeding for

1. any bleeding event, and
2. in-hospital bleeding events.

Table 16: Bleeding events analyzed by admitting specialty				
Admitting specialty	Number (%) N=700	Number (%) per specialty with surgery or cardiac catheterization	Number (%; 95% CI) per specialty any bleeding event	Number (%) per specialty with in-hospital bleeding event
Medicine	143 (20.4)	10 (7.0)	62 (43.4, 35.1-51.9)	13 (9.1, 4.9-15.1)
Cardiology	33 (4.7)	22 (66.6)	15 (45.4, 28.1-63.6)	14 (42.4, 25.5-60.8)
Oncology	68 (9.7)	2 (2.9)	7 (10.3, 4.2-20.1)	4 (5.9, 1.6-14.4)
Hematology	69 (9.9)	0 (0.0)	3 (4.3, 0.9-12.1)	2 (2.9, 0.4-10.1)
General surgery	61 (8.7)	39 (64.9)	20 (32.8, 21.3-46.0)	7 (11.5, 4.8-22.3)
Orthopedic surgery	91 (13.0)	87 (95.6)	14 (15.4, 8.7-24.5)	12 (13.2, 7.0-21.9)
Urology	19 (2.7)	15 (78.9)	8 (42.1, 20.2-66.5)	2 (10.5, 1.3-33.1)
Cardiac surgery	98 (14.0)	96 (98.0)	25 (25.5, 17.2-35.3)	23 (23.5, 15.5-33.1)
Vascular surgery	31 (4.4)	26 (83.9)	9 (29.0, 14.2-48.0)	7 (22.6, 9.6-41.1)
Neurosurgery	10 (1.4)	8 (80.0)	4 (40.0, 12.2-73.8)	4 (40.0, 12.2-73.8)
Thoracic surgery	8 (1.1)	8 (100.0)	1 (12.5, 0.3-52.7)	1 (12.5, 0.3-52.7)
ENT	5 (0.7)	3 (40.0)	2 (40.0, 5.3-85.3)	0 (0.0, 0.0-52.1)
Trauma	19 (2.7)	11 (57.9)	15 (78.9, 54.4-93.9)	0 (0.0, 0.0-21.8)
Gynecology	32 (4.6)	17 (53.1)	14 (43.7, 26.3-62.3)	4 (12.5, 3.5-29.0)
Obstetrics	6 (0.9)	5 (83.3)	6 (100.0, 54.0-100.0)	6 (100.0, 54.0-100.0)
Neonatology	7 (1.0)	0 (0.0)	0 (0.0, 0.0-41.0)	0 (0.0, 0.0-41.0)

 Low risk (<30%) of bleeding event

 Intermediate risk (30-60%) of bleeding event

 High risk (60-100%) of bleeding event

The association between the a priori candidate electronic identifiers and bleeding is explored in Table 17. We added admitting specialty as a post-hoc candidate identifier. Models were developed to predict any bleeding event (Tables 17-20) and an in-hospital bleeding event (Tables 21 and 22). Initially, the significance of all candidate variables was assessed in univariate analysis. A multiple logistic regression analysis was performed with all variables. When modeling all bleeding, co-prescription of anticoagulant and antiplatelet medication was inversely associated with bleeding, which fell counter to our clinical gestalt. Therefore the model was re-run with the medication variable removed, and the C-statistic did not change significantly (Table 19). One further model was run, excluding re-operation as a variable, as a 3 variable model might be easier to develop real-time than a 4 variable model (Table 20).

Table 17: Comparison of candidate variables predicting any bleeding event and in-hospital bleeding events					
Variable	Categories	Proportion (%) with bleeding event who were +ve for variable	Proportion (%) without bleeding event who were +ve for variable	Proportion (%) with in-hospital bleeding event who were +ve for the variable	Proportion (%) without in-hospital bleeding event who were +ve for the variable
Red cell transfusion	1-3 units 4 or 5 units 6 or more units	137/205 (66.8) † 41/205 (20.0) 27/205 (13.2)	472/495 (95.4) 21/495 (4.2) 2/495 (0.4)	57/99 (57.6) † 24/99 (24.2) 18/99 (18.2)	552/601 (91.8) 38/601 (6.4) 11/601 (1.8)
Admitting specialty	*Low risk bleed Intermediate risk bleed High risk bleed	25/205 (12.2) † 159/205 (77.6) 21/205 (10.2)	218/495 (44.0) 273/495 (55.2) 4/495 (0.8)	45/99 (45.5) † 48/99 (48.5) 6/99 (6.1)	477/601 (79.4) 124/601 (20.6) 0/601 (0.0)
Endoscopy	Positive or negative	52/205 (25.4) †	8/495 (1.6)	10/99 (10.1)	50/601 (8.3)
Re-operation	Positive or negative	20/205 (9.8) †	8/495 (1.6)	17/99 (17.2) †	11/601 (1.8)
Antiplatelet and anticoagulant co-prescription	Positive or negative	65/205 (31.7)	196/495 (39.6)	56/99 (56.6) †	205/601 (34.1)
Readmission	Positive or negative	10/205 (4.9)	30/495 (6.1)	6/99 (6.1)	34/601 (5.7)
* For all bleeding events Low risk bleed = hematology, oncology, neonatology, orthopedic surgery, thoracic surgery, oral surgery Moderate risk bleed = general surgery, cardiac surgery, ENT, vascular surgery, general internal medicine, cardiology, gynecology, neurosurgery, urology High risk bleed = trauma, obstetrics For in-hospital bleeding Low risk bleed = general internal medicine, hematology, oncology, neonatology, general surgery, orthopedic surgery, thoracic surgery, oral surgery, trauma, ENT, urology, gynecology Moderate risk bleed = cardiac surgery, vascular surgery, cardiology, neurosurgery High risk bleed = obstetrics † p<0.05					

Building a model for any bleeding

Table 18: Univariate logistic regression analysis of variables predicting any bleeding event					
Variable	Categories	β coefficient	p value	Odds ratio	95% CI
Red cell transfusion	1-3 units	reference		1.0	
	4 or 5 units	1.62	<0.0001	6.7	3.8-8.1
	>5 units	3.84	<0.0001	46.5	10.9-198.1
Admitting specialty	*Low risk bleed	reference		1.0	
	Intermediate risk bleed	5.08	<0.0001	5.1	3.2-5.9
	High risk bleed	3.82	<0.0001	45.8	14.5-144.1
Endoscopy	Positive or negative	3.03	<0.0001	20.7	9.6-44.5
Re-operation	Positive or negative	1.88	<0.0001	6.6	2.8-15.2
Antiplatelet and anticoagulant medication co-prescription	Positive or negative	-0.34	0.05	0.7	0.5-1.0
Readmission	Positive or negative	-0.23	0.54	0.8	0.4-1.7
* Low risk bleed = hematology, oncology, neonatology, orthopedic surgery, thoracic surgery, oral surgery Moderate risk bleed = general surgery, cardiac surgery, ENT, vascular surgery, general internal medicine, cardiology, gynecology, neurosurgery, urology High risk bleed = trauma, obstetrics					

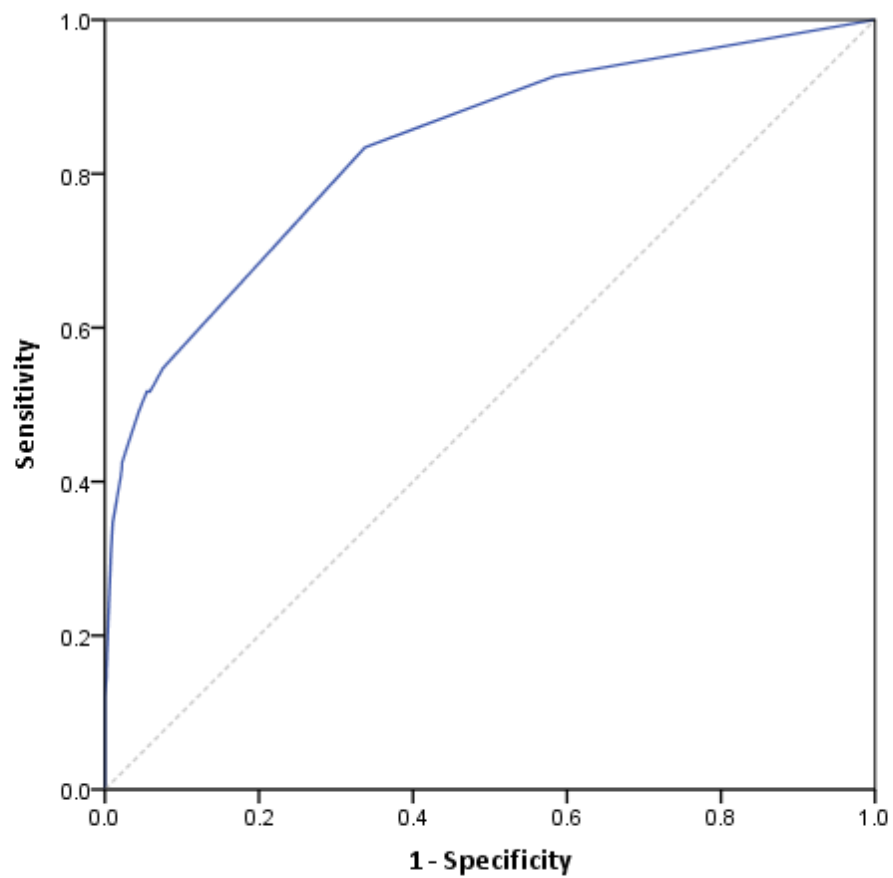
Table 19: Multivariate logistic regression model to predict any bleeding event					
Variable	Categories	β coefficient	p value	Odds ratio	95% CI
Red cell transfusion	1-3 units	reference		1.0	
	4 or 5 units	2.03	<0.0001	7.6	14.6-3.9
	>5 units	3.55	<0.0001	34.9	7.4-164.2
Admitting specialty	*Low risk bleed	reference		1.0	
	Intermediate risk bleed	1.42	<0.0001	4.2	2.4-7.0
	High risk bleed	3.57	<0.0001	35.5	10.6-119.5
Endoscopy +/- 24 hours	Positive or negative	2.89	<0.0001	17.6	7.8-39.8
Re-operation	Positive or negative	1.68	0.001	5.4	2.0-14.7
Antiplatelet and anticoagulant medication co-prescription	Positive or negative	-0.71	0.002	0.5	0.3-0.7
C-statistic 0.84 (95% CI 0.81-0.88)					
* Low risk bleed = hematology, oncology, neonatology, orthopedic surgery, thoracic surgery, oral surgery Moderate risk bleed = general surgery, cardiac surgery, ENT, vascular surgery, general internal medicine, cardiology, gynecology, neurosurgery, urology High risk bleed = trauma, obstetrics					

Table 20: Multivariate logistic regression model excluding 'antiplatelet, anticoagulant' variable					
Variable	Categories	β coefficient	p value	Odds ratio	95% CI
Red cell transfusion	1-3 units	reference		1.0	
	4 or 5 units	1.89	<0.0001	6.6	3.5-12.6
	>5 units	3.33	<0.0001	28.0	6.2-126.9
Admitting specialty	*Low risk bleed	reference		1.0	
	Intermediate risk bleed	1.23	<0.0001	3.4	2.1-5.7
	High risk bleed	3.64	<0.0001	38.0	11.4-127.3
Endoscopy +/- 24 hours		2.98	<0.0001	19.6	8.8-43.8
Re-operation		1.6	0.002	5.0	1.8-13.4
C-statistic 0.82 (95%CI 0.79-0.86)					
* Low risk bleed = hematology, oncology, neonatology, orthopedic surgery, thoracic surgery, oral surgery Moderate risk bleed = general surgery, cardiac surgery, ENT, vascular surgery, general internal medicine, cardiology, gynecology, neurosurgery, urology High risk bleed = trauma, obstetrics					

Table 21: Model performance in predicting any bleeding events		
Model	C-statistic	95% CI
PRBC, specialty and endoscopy only	0.81	0.78-0.85

Figure 9 shows the ROC curve for the four variable model. Although the area under the ROC curve is high, the curve does not extend close towards the upper left corner (it is blunted), so it is difficult to establish an ideal probability cut point at which to determine a positive trigger.

Figure 9: Receiver operating characteristics curve for the 4-variable model predicting any bleeding: red cell transfusion, admitting specialty, endoscopy and return to the operating room.



Area under the ROC curve 0.82 (95%CI 0.79-0.86)

Table 22 shows the ideal model probability cut point for 1. maximizing sensitivity and 2. maximizing specificity.

Table 22: Exploring the optimal probability cut-point for the model to predict any bleeding			
Probability cut-point		Sensitivity (95%CI)	
0.30		83.4% (77.6-88.2%)	
Missed bleeds		False positives	
Operation site	11/50	Internal medicine	81
Gastrointestinal	12/78	Hematology	3
Hematuria	2/15	Oncology	1
Retroperitoneal	1/2	General surgery	4
Hemoptysis	1/3	Orthopedics	7
Vaginal	2/10	Urology	11
Hematoma (skin)	1/8	Cardiac surgery	10
Hematoma (muscle)	1/9	Cardiology	18
Hematoma (abdominal/pelvic)	1/8	Gynecology	18
Epistaxis	2/5	Neurosurgery	6
		Thoracic surgery	1
		ENT	3
		Trauma	4
Total	34	Total	167
Probability cut-point		Sensitivity (95%CI)	
0.55		49.2% (42.1-56.3%)	
Missed bleeds		False positives	
Operation site	23/50	General medicine	7
Gastrointestinal	25/78	General surgery	3
Hematuria	14/15	Cardiac surgery	9
Retroperitoneal	1/2	Gynecology	1
Hemoptysis	3/3	Neurosurgery	2
Intracranial	1/3		
Vaginal	8/10		
Hematoma (skin)	6/8		
Hematoma (muscle)	7/9		
Hematoma (abdominal/pelvic)	4/8		
Epistaxis	4/5		
Postpartum	4/6		
Multiple sites	1/1		
Ruptured ectopic pregnancy	1/2		
Intraperitoneal	1/1		
Hemothorax	1/2		
Total missed bleed	104	Total	22

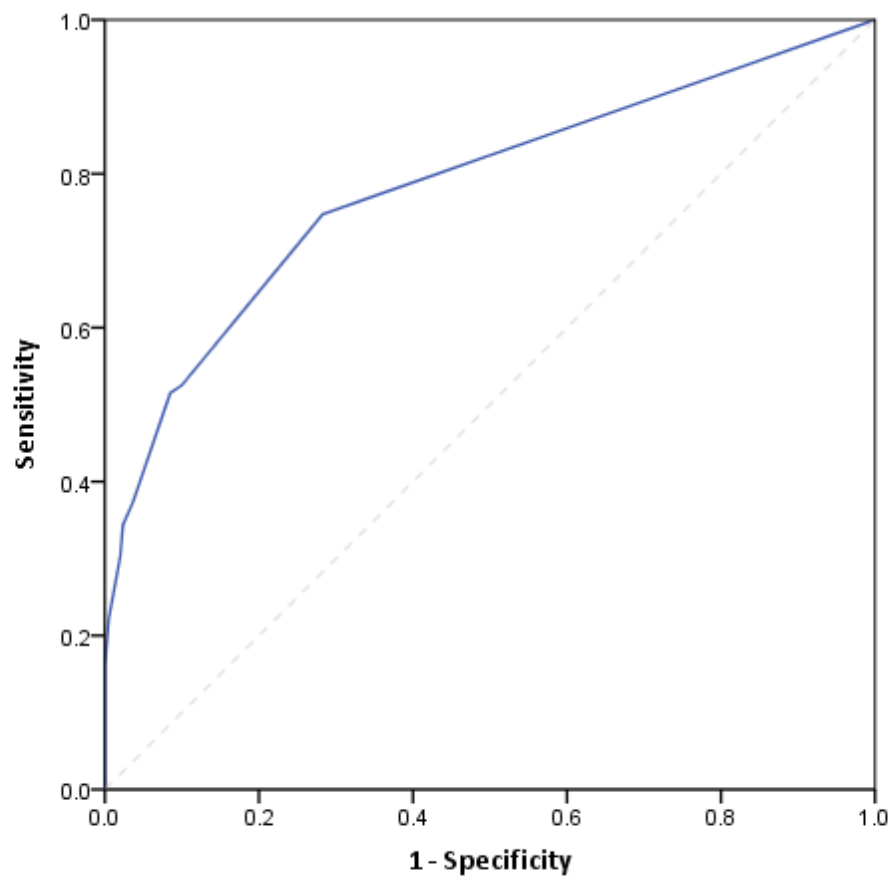
Building a model for in-hospital bleeding

Neither endoscopy nor readmission was associated with in-hospital bleeding (Table 24). The final model with the greatest C-statistic included only PRBC transfusion, specialty and re-operation (Table 25). Figure 9 shows the shape of the ROC curve.

Table 23: Univariate logistic regression analysis of variables predicting in-hospital bleeding event					
Variable	Categories	β coefficient	p value	Odds ratio	95% CI
Red cell transfusion	1-3 units	reference		1.0	
	4 or 5 units	1.8	<0.0001	6.1	3.4-10.9
	>5 units	2.8	<0.0001	15.8	7.1-35.2
Admitting specialty	*Low risk bleed	reference		1.0	
	Intermediate risk bleed	1.4	<0.0001	3.5	2.1-5.9
	High risk bleed	20.3	0.99	†	
Endoscopy	Positive or negative	0.21	0.56	1.2	0.6-2.5
Re-operation	Positive or negative	2.41	<0.0001	11.1	5.0-24.6
Antiplatelet and anticoagulant medication co-prescription	Positive or negative	0.92	<0.0001	2.5	1.6-3.9
Readmission	Positive or negative	-0.18	0.57	0.8	0.4-1.6
* Low risk bleed = general internal medicine, hematology, oncology, neonatology, general surgery, orthopedic surgery, thoracic surgery, oral surgery, trauma , ENT, urology, gynecology Moderate risk bleed = cardiac surgery, vascular surgery, cardiology, neurosurgery High risk bleed = obstetrics † Group too small to calculate OR					

Table 24: Multiple logistic regression analysis of variables predicting in-hospital bleeding event					
Variable	Categories	β coefficient	p value	Odds ratio	95% CI
Red cell transfusion	1-3 units	reference		1.0	
	4 or 5 units	2.0	<0.0001	7.2	3.9-13.4
	>5 units	2.3	<0.0001	9.6	3.9-23.9
Admitting specialty	*Low risk bleed	reference		1.0	
	Intermediate risk bleed	2.2	<0.0001	3.4	2.1-5.7
	High risk bleed	23.5	0.99	†	
Re-operation	Positive or negative	1.9	<0.0001	6.6	2.5-17.5
C-statistic = 0.78 (95% CI 0.73-0.84)					
* Low risk bleed = general internal medicine, hematology, oncology, neonatology, general surgery, orthopedic surgery, thoracic surgery, oral surgery, trauma , ENT, urology, gynecology Moderate risk bleed = cardiac surgery, vascular surgery, cardiology, neurosurgery High risk bleed = obstetrics † Group too small to calculate OR					

Figure 10: Receiver operating characteristics curve for the model predicting in-hospital bleeding: red cell transfusion, admitting specialty and return to the operating room.



Area under the ROC curve 0.78 (95% CI 0.73-0.84)

Table 25 explores the effect of choosing a model probability cut-point to determine a positive bleeding trigger. The maximum sensitivity, with acceptable specificity is achieved with a cut-point of 0.15. The maximum specificity with acceptable sensitivity is achieved with a cut-point of 0.28. Some of the false positive results are actually bleeds which started in the home setting, prior to admission.

Table 25: Exploring the optimal probability cut-point for the model to predict in-hospital bleeding					
Cut-point		Sensitivity		Specificity	
0.15		74.7% (65.0-82.9%)		71.7% (67.9-75.3%)	
Missed in-hospital bleeds		False positives that were outpatient bleeds		False positives that were not bleeds	
Operation site	9/50	Gastrointestinal	17	Medicine	4
Gastrointestinal	8/20	Hemoptysis	1	General surgery	1
Hematuria	4/6	Intracranial	2	Orthopedic	6
Vaginal	2/2	Vaginal	1	Cardiac surgery	73
Hematoma (muscle)	2/6	Hematoma (skin)	1	Cardiology	18
		Hematoma (muscular)	2	Gynecology	1
		Hematoma (abdominal / pelvic)	4	Neurosurgery	6
		Hemopericardium	1	Thoracic	1
		Leaking AAA	1	ENT	3
		Ruptured ectopic pregnancy	1	Vascular	22
		Hemothorax	1	Hematology	3
Total missed bleed	25/99	Total	32/170	Total	138/170
Cut-point		Sensitivity		Specificity	
0.28		51.5% (41.3-61.7%)		91.5% (89.0-93.6%)	
Missed in-hospital bleeds		False positives that were outpatient bleeds		False positives that were not bleeds	
Operation site	17/50	Gastrointestinal	16	Medicine	4
Gastrointestinal	15/20	Intracranial	2	Orthopedic	4
Hematuria	6/6	Hematoma (skin)	1	CABG	5
Vaginal	2/2	Hematoma (abdominal / pelvic)	4	Cardiac valve replacement	5
Hematoma (skin)	2/3	Hemopericardium	1	Hematology	3
Hematoma (muscle)	4/6	Leaking AAA	1	Neurosurgery	2
Hematoma (abdominal/pelvic)	1/1	Ruptured ectopic pregnancy	1	Thoracic surgery	1
Epistaxis	1/2	Hemothorax	1	Gynecology	1
Total missed bleed	48/99	Total	27/51	Total	24/51

Accuracy of the automated electronic variable classification

The chart review was treated as the gold standard classification of each variable. This was compared to the data warehouse automated electronic classification. The 2 x 2 performance tables can be reviewed in Appendix 6. The data warehouse electronic identification performed best for unscheduled readmission, where 100% of cases were correctly classified. The data warehouse electronic identification of number of units of blood prescribed within a twenty four hour period agreed with the chart review in 694/700 cases. The sensitivity and specificity for endoscopy were 93.3% and 94.5%, for re-operation, 46.4% and 99.6%, and for co-prescription of anticoagulation and antiplatelet medication 73.7% and 94.1%.

Since admitting specialty was not a predefined variable (and instead is an ad hoc variable), there was no automated electronic identifier with which to compare the chart search classifications.

Analysis of exploratory cohort bleeding events where no transfusion was prescribed

Table 26 describes the bleeding sites for the bleeding events that were not treated with transfusion.

Table 26: Bleed events not transfused N=160/353 total events				
	Number	%	Bleeding site	
Perioperative bleed	39	25.0	operation site	26
			gastrointestinal	6
			hematuria	1
			retroperitoneal	1
			intracranial	2
			hematoma (skin)	2
			hematoma (muscle)	1
			hematoma (abdominal/pelvic)	1
Spontaneous bleed	120	56.9	gastrointestinal	19
			hematuria	11
			hemoptysis	2
			intracranial	65
			vaginal	4
			hematoma (abdominal/pelvic)	2
			epistaxis	4
			hemothorax	3
			ruptured ectopic pregnancy	1
Perioperative and spontaneous bleed	9	50.0	spontaneous intracranial hemorrhage and perioperative surgical site bleeding	8
			spontaneous retroperitoneal bleed prior to surgical procedure and postoperative repeat retroperitoneal bleed	1

The most striking finding is that a large number of patients with intracranial hemorrhage did not require blood transfusion.

Ad hoc assessment of The Ottawa Hospital ICD-10 coding diagnostic utility

The sensitivity and specificity of the ICD coding for both bleeding and venous thrombosis was assessed (Tables 27 and 28).

Table 27: Diagnostic characteristics of ICD-10 coding: All bleeds		
	Bleed (chart read)	No bleed (chart read)
Bleed (ICD code)	326	179
No bleed (ICD code)	27	406
Sensitivity 92.4% (95%CI 89.1-94.9%)		
Specificity 69.4% (95%CI 65.5-73.1%)		

Table 28: Diagnostic characteristics of ICD-10 coding: Postoperative venous thromboembolism		
	Postoperative VTE (chart read)	No postoperative VTE (chart read)
Postoperative VTE (ICD code)	122	115
No postoperative VTE (ICD code)	6	695
Sensitivity 95.3% (95%CI 90.1-98.3%)		
Specificity 85.8% (95%CI 83.2-88.1%)		

DISCUSSION

Summary

Patient safety is a priority in health care organizations. Bleeding is an adverse occurrence which puts patients at risk of death, MI, acute kidney injury and prolonged hospitalization. To date, there is no prospective method for identifying patients who are bleeding real-time within a hospital organization. We report the derivation of two prediction models to identify hospital bleeding events at The Ottawa Hospital.

We found that the combination of number of units blood transfused, admitting specialty, occurrence of endoscopy and re-operation performed well in identifying bleeding events within a cohort of patients who had a blood transfusion (C-statistic 0.83). We were also able to identify bleeding events which started in hospital with a model using number of units blood transfused, admitting specialty and re-operation.

A real-time electronic trigger for bleeding could be helpful in a variety of ways. First of all it will form the platform for much needed epidemiological data collection: the incidence and distribution of bleeding events within The Ottawa Hospital. Secondly, identification of bleeding events will facilitate further research on how to predict which patients will develop bleeding. Thirdly, multidisciplinary root cause analysis of each bleeding event will identify potential problem areas, or holes in the system, whereby patients may be unnecessarily exposed to risk of bleeding. And finally, an array of interventions could be instigated to mitigate future bleeding events in high risk patients. These could include referral to the anticoagulant clinic for periprocedural anticoagulation, careful risk benefit assessment prior to starting anticoagulation treatment, centralized monitoring of drug levels and renal function, careful patient choice for surgery, choice of surgical technique and much more.

Learning process

This was as much a learning process about the method for producing an electronic identification trigger as it was a model building exercise. The strengths of our method include an exploratory cohort of 1000 recent patient encounters and a model derivation cohort of 700 encounters. Every single patient encounter was examined in detail by a physician with clinical expertise in bleeding, by reading all written and electronic information associated with the encounter. The candidate variables were chosen after discussion with both data warehouse experts and clinical experts, so we expect that the process of

transformation into a robust real-time electronic identifier is possible, and that the included variables make intuitive clinical sense.

We encountered many unforeseen problems in this development process, the majority of which occurred during data extraction from the exploratory cohort. The first and most important issue was the lack of clarity for the gold standard definition of bleeding. This hindered progression of the analysis past the exploratory cohort. An extensive literature review failed to produce a universal, pragmatic definition which could be applied to a retrospective cohort. The BARC criteria⁵⁴ would have provided the most sound definition since it considers bleeding in different sites and scenarios, however it does not give advice on non-cardiac surgical bleeding and it does not give binary outcomes (bleeding present or absent). The ISTH definition^{57;58} covers both surgical and spontaneous bleeding, however it requires that the surgeon gives an opinion as to whether the blood loss is excessive or prolonged. This is not possible in a retrospective case review.

We decided to make our definition relatively broad, in that bleeding only required to have had an intervention or to have prolonged the hospital admission in order to be considered as 'bleeding'. Our criteria for perioperative bleeding required the surgeon to have documented that there was abnormal bleeding. This is a strength because our definition dove tails as much as possible with that of the ISTH, and it will stand up to future scrutiny by The Ottawa Hospital surgeons, however an inevitable consequence is that if the surgeon did not pay enough attention to the bleeding, or else was reluctant to document in writing that the patient lost more blood than expected, we will have misclassified the bleeding outcome. Furthermore, part of the reasoning behind developing an electronic real-time trigger for bleeding was to aid doctors in recognizing that their patient had a bleeding problem. Our current identification model was developed to identify bleeding events where the admitting physician probably already knows their patient is bleeding.

A second unanticipated problem was that some encounters included more than one surgical procedure. In a few instances there were 10 or more operative procedures in a single encounter. This made it difficult to determine if a bleeding event related to one surgery or the other. Furthermore, repeat surgeries compound the blood loss and could lead to several blood transfusions in the space of seven days (a data point collected in the exploratory cohort). It is likely that a patient who has three surgeries in one week will have more blood loss and a patient who has only one of these surgeries. Therefore we took the decision to record details on only the first surgery performed during that encounter. As a result the evaluation of the ICD-10 coding performance in identifying encounters with perioperative bleeding is biased, since we did not capture data on all surgeries.

Thirdly, although each encounter was evaluated for spontaneous bleeding at any point in time during the encounter, it was difficult to collect data on all hemoglobin changes and PRBC transfusions during the encounter. For example, some patients having bone marrow transplants receive a unit PRBC every other day throughout admission, and their hemoglobin will fluctuate up and down. I collected data on the number of PRBC units given after a bleed or surgery, for seven days. When there was neither a bleed nor surgery, it would be impossible to know which seven days to evaluate. Therefore no hemoglobin and transfusion data was collected on patients who did not have surgery and did not bleed. This limited the analysis as the ROC curves assessing these variables as predictors of bleeding did not include data on this subpopulation, and was a source of bias. It is possible that the ROC curves report a higher area under the curve than what we would find in reality. This issue was resolved in the model derivation cohort because we identified the date of transfusion for each encounter, and all charts were evaluated for bleeding in relation to this date.

Fourthly, the original plan was to perform a chart review to ascertain whether each encounter had a bleeding event or not. Demographic data were to be retrieved using an electronic data warehouse search. However it was not possible to obtain these data electronically, so instead we relied on my hand extracted demographics. This restricted the range of variables to those already collected from the exploratory cohort. During the process as much evidence as possible was collected, in order to validate classifying each encounter as bleeding event positive or negative. Therefore during the exploratory cohort data extraction, bleeding verified by endoscopy or necessitating readmission to hospital was specifically recorded. There was no record of whether patients without bleeding had undergone endoscopy or readmission. So when we included endoscopy on the list of candidate variables for the model, it was based purely on the observation that 20% of all bleeding events were from the GI tract, and clinical gestalt that an endoscopy would likely follow a transfusion in a patient with a GI bleed. Readmission was included on the basis that there was already a validated readmission electronic trigger. Finally, our model derivation cohort consisted of all patients who had been transfused. This helped define the event date and standardized the process of data collection. Intuitively, we should have particular interest in transfusion events as we expect there to be a higher probability of a bleeding event. As discussed in the introduction, the act of transfusion may in itself be an adverse outcome, compounding the risks associated with bleeding. However the exploratory cohort recorded 39 perioperative bleeds, 120 spontaneous bleeds and 9 combined where no transfusion was given. In all, 32% of all bleeding events received no blood transfusion. It is difficult to argue that these missed events were not important because they included diagnoses of intracranial, gastrointestinal and surgical bed

bleeding. Although we cannot draw conclusions about the real incidence from the exploratory cohort data, we can expect that some bleeding events are not treated with transfusion. In order for our bleeding trigger to effectively identify all relevant bleeds, the model should be tested on all patients regardless of transfusion.

Why not use ICD coding to report bleeding?

Some may ask why we are spending so much time to invent an identifier for bleeding when the hospital already invests considerable resources in coding all admissions. The Ottawa Hospital employs a group of coders who read through the entire hospital chart and assign relevant ICD-10-CA codes to each hospital admission.

First of all, this happens after the patient has been discharged, therefore we cannot use ICD-10 codes to identify patients who are bleeding real-time.

Secondly, there is scant evidence that the coding system is sensitive and specific for bleeding. In 1999-2000, a case control study performed at The Ottawa Hospital⁹⁸ showed that coding for bleeding was 93% sensitive and 88% specific. However, this was a case control cohort comprising of patients with either with an ICD-9 code for bleeding or for venous / arterial thrombosis. The coding was performed real time in consultation with the admitting physician, in contrast to now when it is performed in retrospect. Another retrospective case control cohort study of US warfarin users was used to identify hospital presentations with ICD coding for bleeding⁹⁹. The authors showed that 165/186 hospital admissions were either for confirmed or probable bleeding episodes (positive predictive value of 89%). There were 19 admissions where bleeding was possible however there was no objective evidence of bleeding in the records, mostly because a decision was taken not to investigate the symptoms. The final two presentations were for patients with prior bleeding who were found to be negative for bleeding on that admission.

In contrast to this, Abraham et al.¹⁰⁰ found the positive predictive value for ICD coded GI bleeding was 27%. They found that adding upper GI endoscopy procedure code to ICD 9 coding for GIB improved the predictive value to 51%. Similarly Wahl et al.¹⁰¹ found that the positive predictive value of codes for upper GI bleeding was 56%. They could improve this by including codes for hemorrhage control and gastric ulcer.

So although ICD-10 coding might be helpful for retrospective analyses, there is not good evidence for its accuracy.

Our own analysis was biased because we included only the first operation during each encounter. However we identified 27 encounters in the exploratory cohort where there was no bleeding code, but there was actually a bleeding event. It is difficult to interpret the 179 encounters identified as having had a bleeding event by coding, but not by the chart search, because we did not include every surgery. In addition, some of ICD codes for bleeding were appropriate for chronic conditions such as menorrhagia or previous gynecological bleeding as well as acute presentation of bleeding. In contrast the ICD coding for venous thrombosis was sensitive (missed very few episodes of venous thrombosis), but the specificity was reduced because of confusion between chronic thromboses, superficial thromboses and thromboses diagnosed at some point prior to admission.

How do our results compare to the literature?

National quality standards

There has been a recent push in the United States to report bleeding as a complication of surgery. The Agency for Healthcare Research and Quality (AHRQ) produced a list of Patient Safety Indicators (PSIs) which are reported as health quality outcomes from surgery. The AHRQ defines perioperative bleeding by analysis of the hospital ICD coding alone. A bleeding event is defined by a hospital encounter with ICD coding for [postoperative hemorrhage or hematoma in a secondary diagnosis field] or [a procedure code of postoperative control of hemorrhage or evacuation of hematoma]. Therefore to fulfill the AHRQ definition of perioperative bleeding a patient must have a recognized bleed from the surgical bed or a re-operation for bleeding. Our definition is much broader. We know that only 67% of perioperative bleeding events in the model derivation set had a surgical bed bleed and that only 27% required re-operation.

The National Surgical Quality Improvement Program (NSQIP) is a United States clinical registry of surgical cases. Unlike the AHRQ PSI measurements, the data is collected prospectively. Their definition of perioperative bleeding is bleeding that requires more than 4 units of blood within the 72 hours following surgery. Again, the definition is more restrictive than ours because they count only the PRBC units given after surgery and require that 5 or more PRBC units are given.

Borzecki et al.¹⁰² examined 4 years of discharge data from 28 Veterans Health Administration hospitals. They identified 112 encounters using the AHRQ PSI perioperative bleeding indicator. Only 84 cases were true postoperative bleeds which equated to a positive predictive value of 75%. So it appears that the

national recommended method for identifying perioperative bleeding in the US does not perform as well as it should.

Comparisons between methods to identify bleeding

Koch et al.¹⁰³ found kappa for perioperative bleeding was poor when defined by AHRQ and NSQIP ($k=0.14$). They also analyzed cardiovascular surgical data from the Cleveland Hospital database. The hospital defines perioperative bleeding by the need for re-operation alone. They showed that the correlations between all 3 definitions are poor (AHRQ and Cleveland $k=0.08$, NSQIP and Cleveland $k=0.29$).

Reporting bleeding as a surgical complication

Cram et al.¹⁰⁴ compared the Katz/Cram and PSI methods for identifying perioperative bleeding in 241,000 medicare beneficiaries who underwent a total hip replacement. The Katz/Cram identification method has not been described in publication. They found the incidence of postoperative bleeding varied depending on the definition: 1.29% for the Katz/Cram method and 0.05% with the PSI method. The rates of bleeding after revision were 3.87% and 0.20% respectively. We cannot compare our own results as we did not study all orthopedic patients, only those who were prescribed blood transfusion. However it seems that no two administrative database methods identify the same patients as bleeding. The chosen method will have considerable impact on the reported quality of care provided by a healthcare institution.

Comparing the distribution of blood transfusions

Our model derivation cohort was a random sample of 12% of patients who were transfused in The Ottawa Hospital over a 16 month period. We found that 40% of the patients who were transfused were admitted under a medical specialty and 14% of patients were admitted in cardiac surgery. This concurs with other literature that around 50% of transfusions go to surgical specialties¹⁰⁵ and that cardiac surgery accounts for 15-20% of all transfusions¹⁰⁶. So although our validation sample size was only 12% of the whole population, it appears to be reflective of normal hospital practice.

In comparison to the published research on identification of bleeding using administrative data, our project appears to be the first to use other electronic information than the ICD coding. There is a dearth of literature with which to compare this project.

Detecting in-hospital bleeding versus detecting all bleeding

During the process of building an electronic trigger, there was some conflict over whether the trigger should only identify bleeds which start in the hospital (and hence are the bleeds which are ‘hospital-acquired’), or whether it is reasonable for a trigger to also identify bleeding events when the patient presents to the emergency with the bleeding. The latter events are less likely to relate to previous hospital treatment, although we know that some patients were readmitted after a prior hospitalization. The main intention is to improve patient safety, therefore identifying the bleeds which occur in hospital seems the logical aim.

However, any electronic identifier for bleeding is likely to identify both events. We found that our in-hospital model identified some outpatient bleeding events, which accounted for between 19 and 53% of all false positive results (depending on the model probability cut-point applied).

When we looked at the demographics of the two populations (in-hospital bleeding and bleeding which starts in the home), there were some important differences. Three quarters of GI bleeds started in the home and there were more patients with hematuria, hemoptysis, epistaxis and vaginal bleeding in this group. All intracranial bleeds started in the home (although in the exploratory cohort, 3 out of 88 intracranial bleeds started in hospital). Catastrophic vascular events such as ruptured abdominal aortic aneurysm, aortic dissection and ruptured ectopic pregnancy started at home. As a result, the specialty bleeding risk categorization changed between the two models. GI bleeds are admitted under medicine or surgery. Both of these specialties were moderate risk for ‘any bleed’ but low risk of ‘in-hospital bleed’. Likewise, all trauma events happened outside the hospital, therefore being transfused while admitted under trauma was associated with high risk of ‘any bleed’ but no risk of ‘in-hospital bleed’. In contrast, all postpartum hemorrhages occurred in patients who delivered in hospital, therefore obstetric transfusion was highly predictive of in-hospital bleeding. Endoscopy was not strongly associated with in-hospital bleeding because only 20% of in-hospital bleeds were from the GI tract, and 10% patients in the ‘no in-hospital bleed’ group had a GI bleed.

Does the distinction between in-hospital bleeding and patients who are admitted with bleeding matter? On one hand it does not. For example, if we alert every admitting physician when the bleeding trigger is positive, they will not be concerned about where their patient started to have the bleed, although they will already know that the patient is bleeding if that was the very reason for admission. On the other hand, if we use the trigger to report the hospital wide incidence of in-hospital bleeding, it is important that we do not artifactually inflate the numbers. In this example we would be using the data to argue that hospital care is not as safe as it should be, because we believe we can avert in-hospital bleeds. There is a further suggestion that it is important to make the distinction because many of the bleeding events starting at home are unlikely have iatrogenic causes (such as ectopic pregnancies, aortic dissections and vaginal bleeding).

The ideal working model

Patients who have a preoperative hemoglobin of 180 may lose 50% of their circulating blood volume without their surgeon prescribing a blood transfusion. In contrast, patients with a preoperative hemoglobin of 90 will most likely be given a blood transfusion in major surgery, as they have no reserve. Furthermore, the recent literature suggesting that transfusions might worsen patients outcomes could lead to variation in the use of transfusion and hemoglobin thresholds. However we can justify using the number of PRBC units instead of the hemoglobin drop or calculated measure of blood loss in our model because the areas under the ROC curves were very similar.

There are several problems with using hemoglobin as an identifier for bleeding. 1. Some patients did not have a preoperative blood count drawn, so the variable cannot be applied in all patients. 2. Although types of surgeries differed in the distribution of the hemoglobin drop, on the whole the spread was more similar between surgeries than that seen with PRBC. This might be explained because we only have so much circulating blood to lose and an acute drop in hemoglobin to below 50g/L may well not be compatible with life. The number of units of blood transfused may be a more sensitive measure of blood loss volume. 3. Most importantly, the number of PRBC is a much easier and simpler variable to measure electronically than changes in hemoglobin.

We found that co-prescription of both antiplatelet and anticoagulant medication was more prevalent in patients who had a bleed in hospital, than those who did not. The opposite was found when we compared the groups with any bleeding event and no bleeding event. The majority of admitted patients are prescribed anticoagulant prophylaxis, so we expect that more patients take both medications when

they are admitted, compared to when they are at home. It is unsurprising that patients who bleed in-hospital were more likely to be prescribed both medications, as the medication causes bleeding. However we did not expect to find that people who had 'any bleed' were prescribed both medications less often than those who had no bleed. The association remained significant in the multivariate model. If we did not have any medical knowledge, we might have left the variable in the model, however there is no possible logical clinical explanation for the finding, and the variable was removed.

We have developed two models: one to predict in-hospital bleeding and another to predict any bleeding. Neither model demonstrated perfect sensitivity or specificity, however the C-statistics are significant. In addition, when we analyzed the false positive encounters, there was a preponderance of cardiac surgery, vascular surgery and cardiology admissions, all specialties where blood loss is a normal part of interventions. There is a hint that perhaps a limitation of our analysis lies in our gold standard definition of bleeding: that we required the admitting physician to acknowledge there was bleeding. Perhaps if the model was operationalized, we would find that most of the positive triggers identified real bleeding events.

Diagnostic utility of the models

The ability for our model to discriminate between patients who are bleeding and those who are not depends on the chosen cut-point threshold. Our choice of cut-point depends on the trigger function. If we want to alert the admitting physician every time the trigger goes off, perhaps we should choose a more specific cut-point, because physicians are easily annoyed with inaccurate and irrelevant information. If we want to follow every bleeding event in the hospital, we would choose a sensitive cut-point so that we miss as few cases as possible. Obviously, this would take more work as someone would have to sift through all the identified patients to ascertain whether they are bleeding or not.

This should be carefully considered prior to operationalizing the electronic trigger. For identification of all bleeding events, a probability cut-point of 0.55 will mean that every identified patient would be very likely to have a bleed. The tradeoff is that the trigger will miss 50% of all the bleeds. If the cut-point is chosen at 0.3, then we will identify 83% of the bleeds, but among those who are identified, only about two thirds will be bleeding. For in-hospital bleeding, a cut point of 0.15 allows us to identify three quarters of all bleeding events in the population, with a false positive rate of around 30%. However, among the false positive encounters, there are several bleeds which started in the home. If we are comfortable to identify these events with the trigger, then the false positive rate lowers to around 20%.

Operationalizing the electronic trigger

In order to operationalize our model, we have to ensure that the automated electronic method for identifying each variable is as sensitive and specific as possible. Real-time identification of the number of PRBC units prescribed should be possible since the electronic record was very accurate. The transfusion prescription is entered real-time, so the identifier could remain the same. Although we do not have any data for automated identification of the admitting specialty, in theory this should work well, since the data was extracted from the same site where the electronic record is updated real-time.

There were two areas where automated identification could be improved. We found that using the presence of an endoscopy report as a proxy marker for an endoscopy was flawed, because these reports can be filed on the electronic medical record under the admission date, instead of the actual date of the endoscopy. We also found that using the operation report as a marker for return to surgery was sub-optimal and 50% of cases were missed. Since the ultimate aim is to produce a real-time trigger, it may be possible to link a completely different event, such as entry into the endoscopy suite or the operating room as a proxy measure.

Weaknesses

It is important to recognize certain limitations in this project. Both the exploratory cohort analysis and the model derivation dataset allowed us to derive the models. All data was retrospective and we have acknowledged the likely issues with determining a gold standard definition for bleeding using retrospective data. Furthermore, the model derivation dataset did not include patients who had a bleeding event and were not transfused, so we do not know whether simply modifying the PRBC variable to include a '0 units' category will help us to identify these patients. We cannot assume that because no transfusion was given, there was not important bleeding. From the exploratory cohort we found intracranial bleeds, retroperitoneal bleeds and GI bleeds among this group.

Further prospective validation among the entire hospital population is required to fully evaluate the models.

Generalizability of the model

There is no national Canadian strategy to unify electronic health records. Each hospital uses software chosen by that particular hospital, and each hospital is moving from paper charts to electronic medical records using a different strategy. There is no nationwide integration. This poses considerable threat to the generalizability of our models, since data that are readily identifiable on The Ottawa Hospital records may not be identifiable in other hospitals. For example, the hospital keeps accurate real-time electronic records of the number of red cell transfusions a patient has been administered. As soon as the used bags are received by the laboratory, the transfusion is documented on the medical record. Other hospitals may not keep their electronic record up to date throughout the day and night.

In addition to the electronic data captured by each hospital, it is possible that other hospitals may have a different approach to bleeding. For example, we found that most patients who have a gastrointestinal bleed in The Ottawa Hospital will undergo upper or lower endoscopy. Many rural hospitals may not have ready access to endoscopy. There may also be different medical cultural norms, where drivers to perform an endoscopy, or to take a patient back to the operating room, vary compared to those in Ottawa. In particular, hospitals in other countries may be more or less interventive in elderly and frail patients.

Lastly, it is likely that other hospitals may vary in the population they serve. Ottawa serves an educated and wealthy population. It is to be expected that other hospitals admit patients with different comorbidities and lifestyle habits. This will further impact on the generalizability of this ETrigger.

Next steps

We used two separate retrospective cohorts to establish models which predict all bleeding and in-hospital bleeding events. There are several options for taking this forward. Our derivation set only included patients who received a transfusion. One option would be to review a third dataset which includes a random selection of hospital patients, to establish whether the models predict bleeding events, even when no transfusion is given. However this would be a huge undertaking given the low incidence of bleeding within the hospital. Another option would be to analyze a set of patients who had a bleeding event, without a transfusion. From our data, this seems more likely to occur in neurosurgical patients, surgical patients and urology patients. Prospective identification of such patients in the wards

would enable analysis to determine whether our model would detect the bleeding. This in turn would lead to iterative modification of the model, to optimize capture of the relevant events.

Once model performance is maximized, the next step in the ETrigger process is to convert each model variable into a real-time electronic identifier within the hospital electronic record system. There will be several options for each variable. For example, during the derivation stage, we used the presence of endoscopy reports and operation reports to identify whether these had taken place. It might be a better option to use entry into the endoscopy suite or the operating room as the real-time trigger.

Following this, prospective validation allows real-time evaluation of the ETrigger performance. Each positive trigger should be assessed by visiting the patient on the ward, to establish whether or not they are having a bleeding episode. The prospective validation process should also include a method for identifying missed bleeding episodes. This might mean visiting all wards each day to ask a senior member of staff if any patients have bleeding, or identifying bleeding patients via their treating physicians. We predict the development process will be iterative in that small changes may be required to the identification algorithm throughout the process, in order to develop a maximally sensitive and specific Etrigger.

CONCLUSION

Patient safety is central to patient care. To date there has been little research about hospital bleeding, there is no standard definition and very little is known about the epidemiology of bleeding. We have developed an Ottawa Hospital definition of bleeding, and we report the derivation of two models to predict all bleeding events and in-hospital bleeding events. We have evaluated the accuracy of the model variables electronically and aim to translate the model into a real-time bleeding trigger. This is the first report of any hospital to use the electronic medical record to tailor its safety standards to reduce bleeding complications.

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APPENDIX

Appendix 1: ICD codes

Table 29: ICD-10 codes for bleeding

Code for bleeding ICD-10	Definition
I85.0	Oesophageal varices
I98.3	Oesophageal varices with other diseases
N92.4	Excessive bleeding premenopausal
N93	Other abnormal uterine or vaginal bleeding
N95.0	Postmenopausal bleeding
N92.1	Excess/frequent menstrual bleeding
R04.0	Epistaxis
R04.1	Hemorrhage from throat
R04.2	Hemoptysis
R04.8	Pulmonary hemorrhage
R04.9	Hemorrhage of respiratory passages other
K29.0	Acute gastritis with hemorrhage
K27.4	Melena with ulcer
K92.1	Melena
K92.2	Gastrointestinal hemorrhage unspecified
K92.0	Hematemesis
M25.0	Hemarthrosis
N02	Recurrent and persistent hematuria
D69.9	Hemorrhagic condition unspecified
R58	Hemorrhage not elsewhere classified
S06.4	Extradural hemorrhage (traumatic)
S06.5	Traumatic subdural hemorrhage
S06.6	Traumatic subarachnoid hemorrhage
H31.3	Choroidal hemorrhage
I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.8, I61.9	Intracerebral hemorrhage
I60.0 – I60.9	Subarachnoid hemorrhage
I62.0	Subdural hemorrhage
I62.1	Extradural (nontraumatic)
I62.9	Intracranial hemorrhage unspecified (nontraumatic)
K22.8	Hemorrhage from the esophagus not specified
H35.6	Retinal hemorrhage
H43.1	Vitreous hemorrhage
K26.0, K26.2, K26.4, K26.6	Duodenal ulcer with hemorrhage
K25.0, K25.2, K25.4, K25.6	Gastric ulcer with hemorrhage

K28.0, K28.2, K26.4, K26.6	Gastroduodenal ulcer with hemorrhage
K62.5	Hemorrhage of rectum and anus
N42.1	Hemorrhage of prostate
T79.2	Traumatic secondary and recurrent hemorrhage
E27.4	Adrenal hemorrhage and infarction
S06.3	Traumatic focal intracerebral haemorrhage
H45.0	Vitreous hemorrhage in diseases classified elsewhere
K22.6	Mallory Weiss
K27.0, K27.2, K27.4, K27.6	Peptic ulcer with hemorrhage
N93.0	Post coital bleeding
T81.0	Postoperative bleed or hematoma
R31	Unspecified hematuria

Table 30: ICD-10 codes for venous thrombosis

Venous thrombosis ICD-10 codes	Definition
I80.0	Deep vein thrombosis
I80.1	Deep vein thrombosis
I80.2	Deep vein thrombosis
I80.3	Deep vein thrombosis
I80.8	Deep vein thrombosis
I80.9	Deep vein thrombosis
I26.0	Pulmonary embolism with cor pulmonale
I26.9	Pulmonary embolism without cor pulmonale
O08.2	Pulmonary embolism following abortion / ectopic / molar pregnancy
O88.2	Obstetric or puerperium pulmonary embolism

Appendix 2: Exploratory cohort specialties

Table 31: Admitting specialties for exploratory cohort

Admitting specialties for exploratory cohort			
Specialty	Number N=938	% total cohort	Surgery
Medicine	191	20.4	157 no surgery 11 general surgery 6 orthopedic surgery 4 other surgery 3 thoracic surgery 3 ENT surgery 2 urology 2 neurosurgery 1 plastic surgery 1 gynecology surgery 1 cardiac surgery
Neurosurgery	115	12.3	97 brain surgery 13 no surgery 5 spinal surgery
General surgery	115	12.3	66 laparotomy 25 laparoscopic surgery 17 no surgery 4 other surgery 2 orthopedic surgery 1 vascular surgery
Orthopedics	100	10.0	62 hip/knee arthroplasty or fracture surgery 24 orthopedic other surgery 4 no surgery 9 spinal surgery 1 general surgery
Obstetrics	70	7.5	48 no surgery 21 obstetric surgery 1 orthopedic surgery
Cardiology	69	7.4	34 cardiac catheterization or pacemaker 20 no surgery 14 valve replacement surgery 1 orthopedic surgery
Gynecology	63	6.7	59 gynecology surgery 3 no surgery 1 general surgery
Cardiac surgery	63	6.7	36 coronary artery bypass grafting 26 cardiac valve surgery 1 no surgery

Admitting specialties for exploratory cohort (continued)			
Specialty	Number	%	Surgery
Urology	58	6.2	39 urology surgery (not radical prostatectomy) 12 radical prostatectomies 7 no surgery
Vascular surgery	46	4.9	44 vascular surgery 2 no surgery
Thoracic surgery	18	1.9	13 thoracic surgery 4 no surgery 1 general surgery
ENT	17	1.8	14 ENT surgery 3 no surgery
Trauma	10	1.1	8 orthopedic surgery 1 neurosurgery 1 no surgery
other	3	0.3	1 plastic surgery 1 neurosurgery 1 no surgery

Appendix 3: Comparisons of bleeding locations in exploratory cohort

Table 32: Comparison of bleeding sites by surgery (exploratory cohort)

Comparison of bleeding sites by surgery (exploratory cohort)		
Bleeding site in exploratory cohort	Post surgery or cardiac catheterization N=691	No surgery / pre-surgery / >30 days after surgery N=247
Operation site	123	0
Gastrointestinal	16	63
Hematuria	1	20
Retroperitoneal	2	5
Hemoptysis	0	4
Intracranial	3	88
Vaginal	1	6
Hematoma (skin)	4	1
Hematoma (muscular)	2	6
Hematoma (abdominal / pelvic / visceral)	3	3
Hemopericardium	1	0
Epistaxis	0	5
Aortic dissection	0	5
Postpartum	0	0
Leaking AAA	0	1
Ruptured ectopic pregnancy	0	1
Adrenal	0	1
Hemothorax	0	5
Site undetermined	1	0

Table 33: Comparison of spontaneous bleeding sites by admission status (exploratory cohort)

Comparison of spontaneous bleeding sites by admission status (exploratory cohort)		
Bleeding site for spontaneous bleeds	Bleed started as outpatient N=185	Bleed occurred while admitted to hospital N=29
Gastrointestinal	53	10
Hematuria	17	3
Retroperitoneal	2	3
Hemoptysis	2	2
Intracranial	85	3
Vaginal	4	2
Hematoma (skin)	0	1
Hematoma (muscular)	5	1
Hematoma (abdominal / pelvic / visceral)	1	2
Epistaxis	3	2
Leaking AAA	1	0
Adrenal	1	0
Ruptured ectopic pregnancy	1	0
Aortic dissection	5	0
Hemothorax	5	0

Appendix 4: Comparison of bleeding locations in the model derivation cohort

Table 34: Comparison of bleeding sites by surgery (model derivation cohort)

Comparison of bleeding sites by surgery (model derivation cohort)		
Bleeding site	Post surgery or cardiac catheterization N=89	No surgery N=116
Operation site	50	0
Gastrointestinal	8	70
Hematuria	5	10
Retroperitoneal	1	1
Hemoptysis	1	2
Intracranial	1	2
Vaginal	3	7
Hematoma (skin)	2	6
Hematoma (muscular)	6	3
Hematoma (abdominal / pelvic / visceral)	2	6
Hemopericardium	1	0
Epistaxis	1	4
Postpartum	5	1
Leaking AAA	1	0
Multiple sites	0	1
Ruptured ectopic pregnancy	1	1
Intraperitoneal	0	1
Hemothorax	1	1

Table 35: Comparison of bleeding site by in-hospital versus outpatient bleeding (model derivation cohort)

Comparison of bleeding site by in-hospital versus outpatient bleeding (model derivation cohort)		
Bleeding site	Bleed started as outpatient	Bleed occurred while admitted to hospital
Operation site	0	50
Gastrointestinal	58	20
Hematuria	9	6
Retroperitoneal	1	1
Hemoptysis	3	0
Intracranial	3	0
Vaginal	8	2
Hematoma (skin)	5	3
Hematoma (muscular)	3	6
Hematoma (abdominal / pelvic / visceral)	7	1
Hemopericardium	1	0
Epistaxis	3	2
Postpartum	0	6
Leaking AAA	1	0
Multiple sites	1	0
Ruptured ectopic pregnancy	2	0
Intraperitoneal	0	1
Hemothorax	1	1

Appendix 5: Analysis of bleeding events by surgical specialty (model derivation cohort)

Table 36: Description of bleeding events by surgical procedure

Description of bleeding events by surgical procedure			
Surgery type	Number of patients	Number per surgery having bleeding event	% (95% CI) per surgery having bleeding event
hip / knee arthroplasty or fracture surgery	73	8	11.0 (4.9-20.5)
other orthopedic	16	5	31.2 (10.0-58.6)
cardiac valve replacement	51	14	27.5 (15.9-41.8)
other cardiac surgery	55	15	27.3 (16.2-41.0)
prostatectomy	6	1	16.7 (0.4-64.2)
other urology surgery	9	3	33.3 (7.5-70.0)
general laparoscopic surgery	4	2	50.0 (6.7-93.2)
general surgery	36	4	11.1 (3.1-26.1)
gynecology	17	8	47.1 (23.0-72.2)
obstetrics	5	5	100.0 (47.8-100.0)
neurosurgery	8	2	25.0 (3.2-65.1)
spinal surgery	7	1	14.3 (0.4-57.9)
thoracic surgery	9	2	22.2 (2.8-60.0)
ENT	7	2	28.6 (3.7-71.0)
oral surgery	1	0	0.0 (0.0-97.5)
vascular surgery	28	9	32.1 (15.8-52.3)
other surgery	1	0	0.0 (0.0-97.5)
cardiac catheterization	16	8	50.0 (23.8-76.1)
no surgery	351	116	33.0 (28.1-38.1)

Appendix 6: Performance of the data warehouse automatic identification of candidate electronic variables

Endoscopy within -24 hour and +24 hours of transfusion

Table 37: Identifying endoscopy

Identifying endoscopy		
	Endoscopy (chart read)	No endoscopy (chart read)
Endoscopy (automated identification)	56	35
No endoscopy (automated identification)	4	605
Sensitivity 93.3% (95%CI 83.8-93.1%)		
Specificity 94.5% (95%CI 92.4-96.1%)		

In 21 encounters, the endoscopy report was filed in the electronic medical records under the day the patient was admitted to hospital rather than the day the endoscopy was performed. Frequently there were two document types for each endoscopy: the hand written report and the letter. The hand written report was sometimes filed under the admission date with the letter correctly entered as the day of the procedure. In one encounter a bronchoscopy was performed on the same day as a transfusion, not and endoscopy.

Re-operation within 7 days of primary surgery

Table 38: Identifying re-operation

Identifying re-operation		
	Re-operation (chart read)	No re-operation (chart read)
Re-operation (automated identification)	13	3
No re-operation (automated identification)	15	699
Sensitivity 46.4% (95%CI 27.5-66.1%)		
Specificity 99.6% (95%CI 98.8-99.9%)		

In 10 encounters the patient had re-opening and repeat surgery on the same day as the initial surgery. None of these were captured as re-operations. In 3 of these encounters there was only one operation

report which either described all surgeries, or else the repeat surgery was only documented in the hand written chart. The other 7 surgeries had an operation report for each re-operation. In 2 encounters there were 2 separate operation reports by different surgeons who participated in the same operation. One patient had re-operation but their initial surgery was performed at a different hospital. In one encounter the operation report was wrongly electronically filed under the admission date and not the date of the operation.

Unscheduled readmission

Table 39: Identifying unscheduled readmission

Identifying unscheduled readmission		
	Readmission (chart read)	No readmission (chart read)
Readmission (automated identification)	105	0
No readmission (automated identification)	0	595
Sensitivity 100.0% (95%CI 96.5-100.0%) Specificity 100.0% (95%CI 99.4-100.0%)		

In all instances the automated electronic identifier was able to distinguish between an unscheduled readmission, a scheduled readmission and no readmission.

Co-prescription of antiplatelet and anticoagulant medication

Table 40: Identifying co-prescription of antiplatelet and anticoagulant medication

Identifying co-prescription of antiplatelet and anticoagulant medication		
	Both prescribed on day of transfusion (chart read)	Both not prescribed on day of transfusion (chart read)
Both (automated identification)	115	32
Not both (automated identification)	41	512
Sensitivity 73.7% (95%CI 66.1-80.4%) Specificity 94.1% (95%CI 91.8-95.9%)		

It was difficult to establish any pattern as to why the automated data warehouse electronic search misclassified a proportion of encounters.

Number of PRBC units prescribed in 24 hours

Table 41: Identifying the number of PRBC units prescribed in 24 hours

Identifying the number of PRBC units prescribed in 24 hours	
Chart read and automated identifier recorded same number of PRBC units	694
Chart read recorded more units	6
Chart read recorded less units	0

Table 42 gives details of discordant results. No causal pattern was found for the discordant results.

Table 42: Comparing chart read to electronic search

Identifying the number of PRBC units prescribed in 24 hours																		
Number of PRBC identified by automated electronic search	Number of PRBC identified by chart read																	
	1	2	3	4	5	6	7	9	10	11	12	14	16	17	18	23	46	
	1	208	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	209
	2	0	348	1	2	0	0	0	0	0	0	0	0	0	0	0	0	351
	3	0	0	51	0	0	0	0	0	0	0	0	0	0	0	0	0	51
	4	0	0	0	44	0	0	0	0	0	0	0	0	0	0	0	0	44
	5	0	0	0	0	16	0	2	0	0	0	0	0	0	0	0	0	18
	6	0	0	0	0	0	12	0	0	0	0	0	0	0	0	0	0	12
	7	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	2
	9	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	2
	10	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	2
	11	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1
	12	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1
	14	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	2
	16	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
	17	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
	18	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1
	23	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
	46	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
		208	348	53	46	16	12	4	2	2	1	1	2	1	1	1	1	700