Derivation of a Clinical Decision Tool for Predicting Adverse Outcomes among Emergency Department Patients with Lower Gastrointestinal Bleeding

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Abstract

Lower gastrointestinal bleeding (LGIB) can result in serious adverse events. Appropriate risk stratification of LGIB patients can improve their care. Previous risk scores to identify severe LGIB patients have limitations, therefore we developed clinical decision tool to accurately identify LGIB patients presenting to the emergency department (ED) who are at risk for 30-day adverse outcomes that would overcome these limitations.

We conducted a health records review and compared two methods of regression analysis on our data in order to develop a clinical decision tool. We identified five risk factors that have a high sensitivity and good predictive value for identifying low risk LGIB patients: age $\geq$ 75 years, INR $\geq$2.0, hemoglobin $\leq$ 100 g/l, ongoing bleeding in the ED and a medical history of colorectal polyps. Future, large, prospective studies should be done to validate the results, after which implementation studies should be conducted.

Executive summary

Background: Lower gastrointestinal bleeding (LGIB) can result in serious adverse events including recurrent bleeding, need for intervention to control the bleeding and/or death. Endoscopy plays a major role in the management of acute LGIB patients; however not all gastroenterologists have appropriate resources to offer adequate endoscopy to patients who might need acute intervention.
Objectives: To develop a highly sensitive and highly specific clinical decision tool to accurately identify LGIB patients presenting to the emergency department (ED), who are at risk for 30-day serious adverse events.
Methods: Design: This is a health records review **Subjects:** 372 adult ED patients with a primary complaint of bleeding per rectum for <3 days and fulfill any of the following: bright red blood per rectum as per history or on the glove after digital rectal examination, or clear red bloody stool during the ED visit were included. **Outcomes:** 30-day composite outcome of all-cause death, recurrent LGIB, need for intervention to control for the bleeding and severe adverse events resulting in admission. **Data collection**: Data on predictors, including ED variables from history, physical examination and laboratory values were collected by one research assistant, and 10% of the predictors were collected by a second independent research assistant. Health records from the Ottawa Hospital and local hospitals in Ottawa, endoscopy reports of the Star Endoscopy Clinic and the Coroner's office were reviewed to assess if adverse events occurred. **Analysis:** Backwards multivariable logistic regression analysis and SELECTION=SCORE option were used to develop a clinical decision tool. We tested the diagnostic accuracy of the final model.
Results: Age ≥75 years, hemoglobin ≤100 g/L, International Normalized Ratio (INR) ≥2, a bloody stool in the ED and a past medical history of colorectal polyps were significant predictors in the multivariable regression analysis. The ROC was 0.83 (95% CI 0.77-0.89), sensitivity 0.96 (0.90-1.00) and specificity 0.53 (0.48-0.59) for a cut-off score of 1.
Conclusion: This model showed good ability to discriminate patients with and without serious outcomes as evidenced by the high Area Under the Curve (AUC) curve and sensitivity. Future, large prospective studies should be done to derive a clinical decision tool after which it should be validated and implemented.

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1. Background

1.1 Introduction

Annually, approximately 20-87 per 100,000 adults are hospitalized because of a lower gastrointestinal bleed (LGIB) (1-3). Patients who are at risk for recurrent bleeding and patients who are in need for intervention to control the hemorrhage need to be properly identified to prevent morbidity and mortality due to further blood loss.

Endoscopy plays a major role in identifying the site and diagnosing the etiology of the bleeding, and applying intervention to stop the bleeding. It is remarkable that 38% of gastroenterologists who perform after-hours endoscopy do not have a trained nurse available, and that 62% do not have access to appropriate anaesthesia (e.g. propofol) after-hours (4).

A clinical decision tool that accurately identifies LGIB patients who appear stable in the emergency department (ED) but are at risk of experiencing serious adverse outcomes after discharge, and who therefore might benefit from in-hospital and urgent management, will help ED physicians to make safe disposition decisions for these patients. Four previous decision tools, an artificial neural network and an algorithm have been developed to aid physicians in risk-stratification of LGIB patients; however none have been adopted into clinical practice (5-10). The main reasons for non-adoption of these tools are likely due to small sample size, not all ED LGIB patients were included and the tools are not easy to use.

The aim of this study was to develop a clinical decision tool that accurately identifies LGIB patients who are at high risk of experiencing 30-day adverse outcomes, such as death, recurrent bleeding or who are in need for an intervention. This will aid ED physicians in their disposition decision-making.

1.2 Definition

A lower gastrointestinal bleeding is classically defined as an intestinal bleed distal to the ligament of Treitz and can clinically be described as hematochezia, bright red blood per rectum or rectal bleeding (11, 12). However, recent literature refers to a lower gastrointestinal bleeding as a bleed

distal to the ileocecal valve (13, 14). *Acute* LGIB is defined as a bleed with an onset of <3 days, and may result in hypotension and tachycardia, with subsequent anemia or need for blood transfusion, and rarely cardiac arrest or death (11, 12, 14).

1.3 Epidemiology

Lower gastrointestinal bleeding is a common problem; a questionnaire among 1,620 adults (20-90 years) living in the United Kingdom reported that 20% of the respondents had experienced a rectal bleeding at least once in their lifetime (15). The estimated proportion of LGIB patients who require hospitalization varies from 20 to 87 per 100,000 adults per year (1-3). There is a lack of robust data regarding the overall incidence of LGIB.

The proportion of LGIB patients requiring hospitalization increases with age. Longstreth reported an incidence rate of 1.0 per 100,000 for individuals in their third decade of life and an incidence rate of 200 per 100,000 in those over the age of 80 (1). A more recent study, published by Hreinsson et al., also showed this age-related trend with an incidence of 18 per 100,000 for people between 25 and 39 years of age and 690 per 100,000 for people over the age of 80 (3).

1.4 Etiology

With this age-related increase in incidence, it follows that the etiology of LGIB is also linked to the prevalence of diseases among the elderly. Diverticular is the most common source of LGIB, as it accounts for 24-47% of the bleeds (2, 6, 12, 14, 16-18). The prevalence of diverticulosis increases with age; it affects 1-2% of people under the age of 30 and up to two-thirds of people who are 80 years or older (19). The cumulative risk of a rebleeding after a diverticular bleed is 25% within 4 years (1, 18) and the recurrence of bleeding after endoscopic intervention for a diverticular bleeding varies from 0-38% (20, 21). Other causes of LGIB are cancer and polyps (6-36%), colitis and ulcers (2-30%), angiodysplasias (3-21%) and a bleeding after polypectomy (5%) (1, 2, 6, 16-18). Anorectal conditions like haemorrhoids, anal fissures and rectal ulcers account for 0-14% of LGIB (6, 12, 17, 18, 22). The use of nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin increases the risk of bleeding in the lower gastrointestinal tract (22-24). Nagata et al. conducted a prospective study to compare NSAIDs, aspirin, other antiplatelet and anticoagulant drug use in patients with and without a LGIB (24). They reported that LGIB patients were more likely to use NSAIDs, aspirin, ticlopidine or clopidogrel than patients without a bleeding, but they found no difference in warfarin and dabigatran use between the two groups.

1.5 Adverse outcomes

Lower gastrointestinal bleeding is a serious condition associated with various clinical important adverse outcomes. The incidence of recurrent bleeding while being hospitalized after a first LGIB episode is 17-20% (6, 25-27). While up to 76% of the LGIB resolve spontaneously, between 2.6% and 24% patients are in need for surgical intervention to control the hemorrhage (1, 6, 25, 27-29). The mortality rate after LGIB is found to be <5% (1, 6, 7, 22, 25-27). Patients who experience LGIB while being admitted to the hospital for another cause have a higher mortality rate compared to patients who are admitted to the hospital with LGIB. This is probably due to the higher comorbidity of patients who are already hospitalized for another cause (1).
Navaneethan et al. conducted a large database study using the Nationwide Inpatient Sample where they included 58,296 patients who were discharged with a diagnosis of LGIB (30). Besides in-hospital mortality and blood transfusion, this study also reported the incidence of other adverse events: acute renal failure (5.9-9.1%), dialysis (2.1-3.2%), acute respiratory failure (1.1-1.6%), hypovolemia/shock (<1%), endotracheal intubation (<1%) and mechanical ventilation for >96h (<1%).

A more common result of LGIB is the need for packed red blood cell (PRBC) transfusion to supplement the blood volume. Approximately 46% of LGIB patients require more than two units of PRBC, 30% require more than four units and 17% require more than six units of PRBC following a bleed from the lower gastrointestinal tract (7). Although receiving a blood transfusion might not seem as clinically important as need for endoscopic or surgical intervention, or mortality, it is an indicator of a more severe bleeding and suggests that the patient requires further monitoring and management and often cannot safely be discharged home without further care.

1.6 Current practice

1.6.1 Initial management

History and physical examination are important to differentiate between a lower and upper gastrointestinal bleeding, to assess the vital signs and to evaluate the severity of the bleeding. Along with this, fluid resuscitation should take place. Isotonic crystalloid solutions and blood products should be infused to maintain a systolic blood pressure (SBP) of >100 mmHg. Patients should receive transfusion with PRBC to maintain a haemoglobin level above 70 g/dl, or above 90 g/dl in case of a massive bleeding, cardiovascular comorbidity, or delay in receiving therapeutic

interventions (31-33). Elderly patients, those with recurrent bleeding, and hemodynamic changes will benefit most from inpatient management and urgent evaluation (14, 32).

1.6.2 Imaging

Radionuclide imaging can aid in identifying the site of an active bleeding, which is helpful as this site is not always clear after history and physical examination. However, this form of imaging does not play a role in assessing the etiology of the bleed or applying intervention to stop the bleeding (32).

Mesenteric angiography can be used for hemostasis in LGIB patients, by injecting vasoconstrictors and/or by embolizing the arterial braches distal from the bleed. This type of intervention mainly plays a role in patients with a massive bleeding that can not be stabilized or reached by endoscopy (32).

1.6.3 Role of endoscopy

Endoscopy can play a major role in the management of LGIB patients as it can identify the source of bleeding and can aid in administering therapeutic intervention to control the bleeding (14). The type of intervention depends on the etiology and severity of the bleeding, the comorbidity status of the patient and experience of the physician. It can include injecting epinephrine, applying a thermal probe and/or applying endoscopic clips over the bleeding site for an active bleeding, or using rubber band ligation or sclerotherapy for internal actively bleeding haemorrhoids (32).

Even though endoscopy plays a major role in both diagnosing and treating patients with LGIB, it is remarkable that 38% of Canadian gastroenterologists who perform after-hours endoscopy do not have a trained endoscopy nurse available for procedures and that 62% do not have access to propofol sedation during after-hours. Sixty-four percent of the gastroenterologists have a registered nurse present during after-hours endoscopy, and 35% had a resident available to aid with the procedure. However, it is important to have trained staff in order to help with administration of sedation, patient monitoring, documentation and technical assistance (4). Therefore, the above-mentioned numbers are concerning as they indicate that only limited health care resources are available for patients who might need acute intervention, which could jeopardize patient safety.

A clinical decision tool could aid ED physicians in their management decisions, by identifying high-risk patients who are in need for urgent intervention and who will benefit from being transferred to a hospital with appropriate access to after-hours endoscopy. It will also aid ED physicians in determining which patients are at low-risk of experiencing adverse outcomes and could be managed in an out-patient setting.

1.7 Costs

Comay and Marshall published a study in 2002 using data from 1994-1996 to assess the costs of admissions due to LGIB (34). In two academic and two community hospitals in Ontario, Canada, they identified 124 patients who were admitted with LGIB. During the mean length of stay of 7.5 days (SD 12.0), a mean of 6.7 (SD 7.2) complete blood counts were done and 1.1 (SD 2.2) coagulation profiles were performed per patient. Eighty percent of the patients underwent an endoscopy, and 10% had a surgery done to control for the hemorrhage or for a recurrent hemorrhage. The overall mean cost was CAD 4,832 per admission (SD CAD 7,187). Patients who were 75 years and older spent on average 11.8 days in the hospital and were accounted for a mean cost of CAD 7,167, while younger patients spent only 6.0 days in the hospital, which was associated with mean costs of CAD 4,020 per admission.

1.8 Methodological Standards for Clinical Decision Tools

We intended conduct a pilot study to develop a clinical prediction tool that combines multiple predictors to estimate the probability of serious outcome occurrence in the short-term (within 30-days) (35, 36). A clinical decision tool is derived from original research, includes three or more variables from the history, physical examination or simple tests like laboratory values, and aims to help clinicians with decision-making (37, 38). The different stages in the development and validation of a clinical decision tool are summarized here (37, 39):

1. There must be a need for the clinical decision tool. A prevalent condition, variability in clinical practice among similar physicians and evidence that physicians feel that the current practice is lacking efficiency are all factors that contribute to the need for a clinical decision rule.
2. The outcome of interest should be of clinical importance, clearly defined and assessed in a blinded setting, without knowledge of the predictor variables (37).
3. Predictor variables should be clearly defined as well, and should also be assessed without knowledge of the outcome. Ideally they should be prospectively collected. However, for this study

predictor variables will retrospectively collected for feasibility. Predictor variables should be reliable, i.e. they have to be consistent and reproducible.

4. Inclusion and exclusion criteria, the method of patient selection, patient characteristics and study setting should be well described in order for physicians to understand the generalizability and applicability of the decision rule.
5. The number of patients enrolled in the study should be justified with a sample size calculation.
6. Mathematical techniques should be described and justified.
7. Decision rules should be sensible; they should be clinically reasonable and easy to use.
8. The accuracy of the tool, along with the sensitivity, specificity, positive predictive value and negative predictive value should be presented.
9. After a clinical decision rule is developed, it should be prospectively validated in a new patient population. Validation studies assess the efficacy or accuracy of the rule.
10. The next phase should be an implementation study, where the effectiveness of the decision rule in the clinical practice is evaluated.

1.9 Previous decision tools

Previously, four predictive models (5-8), one artificial neural network (9) and one algorithm (10) have been developed to predict adverse outcomes after LGIB or to identify patients with severe LGIB. Characteristics of the decision tools, as well as the limitations, are summarized in table 1 and are discussed below.

1.9.1 BLEED

In 1995, the BLEED score was developed, where BLEED stands for ongoing **b**leeding, **l**ow systolic blood pressure (SBP), **e**levated prothrombin time, **e**rratic mental status and unstable comorbid **d**isease (5). This score was developed using a mixed cohort of both acute UGIB and LGIB patients who were admitted to the intensive care unit (ICU). The site of bleeding was determined using diagnostic procedures (endoscopy, angiography, scintigraphy) or by clinical criteria (e.g. passage of bright red blood per rectum). The objective of this score was to predict in-hospital outcomes, defined as a) hospital length of stay; b) surgery to control the hemorrhage; c) rebleeding; d) units of transfused packed RBC's; e) Organ System Failure Index; f) overall mortality. Patients were classified as being at low-risk or at high-risk for experiencing these outcomes. Low-risk patients were defined as being hemodynamically stable before admission to ICU, not requiring vasopressors, not having other organ system derangements requiring intensive

care and not having evidence of active ongoing gastrointestinal hemorrhage at the time of triage. The total cohort consisted of 103 admitted patients, of whom 13 had a LGIB confirmed by endoscopy.
This score was validated in the year 1997 among 465 patients with an acute gastrointestinal bleeding who were admitted to either the ICU ward or any other ward, and 177 (38%) of these patients had a lower gastrointestinal tract bleeding (25). The main outcome differed slightly from the outcome used in the derivation cohort, and consisted of recurrent GI hemorrhage, surgical laparotomy to control the bleeding and mortality.

The derivation study does not specify the accuracy of the BLEED score, and the validation score reports an area under the curve (AUC) of 0.72 but does not specify confidence intervals. An AUC of 0.72 indicates that the BLEED score has a moderate ability to predict in-hospital complications in patients admitted with a gastrointestinal hemorrhage. Another limitation is that the risk score was developed and validated in small patient cohorts with only 13 and 177 LGIB patients respectively. Lastly, the BLEED score is applicable to patients who are admitted to the ICU with LGIB, which decreases the generalizability and usefulness of this tool for all ED LGIB patients.

1.9.2 Strate et al.

Strate et al. developed a risk score for LGIB patients in 2003 and validated this score in 2005, consisting of a) heart rate ≥ 100 bpm; b) systolic blood pressure ≤115 mmHg; c) syncope; d) bleeding in the first 4h of evaluation; e) non-tender abdominal examination; f) aspirin use; g) >2 active comorbid conditions according to the Charlson Comorbidity Index. They aimed to identify patients with severe LGIB, defined as continued bleeding in the first 24 hours and/or recurrent bleeding after 24 hours of stability (6, 27).

In the derivation cohort, data of 252 patients who were admitted with acute LGIB were retrospectively collected, and 49% of the patients experienced a severe bleeding. The validation cohort consisted of 275 patients, of whom 132 patients (48%) experienced an adverse outcome. The AUC was 0.76 in this derivation cohort and 0.75 in the validation cohort (95% confidence intervals were not reported), which indicates a moderately ability to discriminate patients with severe bleeding. It also implies that there might be additional, unidentified, risk factors that play a role in identifying patients with severe LGIB. The studied sample size is small, mortality and need for intervention were not included as primary outcomes, and the risk score is not applicable to all

patients presenting to the ED with acute LGIB, as patients who were discharged from the ED were excluded from the derivation and validation cohorts. Therefore, this risk tool is suboptimal for use in clinical practice.

1.9.3 Velayos et al.

Velayos et al. prospectively developed a risk score in 2004 in ED LGIB patients, to identify those who had a severe LGIB. The risk score consisted of initial hematocrit ≤35%; presence of abnormal vital signs (SBP <100 mmHg or HR >100/min); and gross blood on initial rectal examination. Severe LGIB was defined as an ongoing bleeding or rebleeding after leaving the ED, further defined as a clinically evident gross rectal bleeding associated with abnormal vital signs (SBP <100 mmHg or HR >100/min) or with a transfusion of >2 units of PRBCs during hospitalization.

Ninety-four patients were included, and 37 (39%) of them were classified as having severe LGIB. The authors reported that the three variables (hematocrit, vital signs and rectal examination) were independent predictors of LGIB and that the likelihood of severe bleeding increased with the number of risk factors. However, no diagnostic were reported. Further, the score was developed in a small patient cohort consisting of 94 patients and is not validated. Hence, these criteria cannot be applied in clinical practice.

1.9.4 Artificial Neural Network model

An artificial-neural-network (ANN) model was developed in 2003 in order to identify patients admitted with LGIB who were at risk for in-hospital death, recurrent bleeding or who were in need for endoscopic, radiological or surgical intervention to control the bleeding (9). Artificial-neural-network models are computational networks which try to simulate the networks of neurons in the central nervous system (40). The aim is to expose previously unrecognised relations between input and output variables, using processing units which are interconnected via a set of weights (9, 41, 42).

The cohort that was used to train the ANN model consisted of 120 patients; the ANN model was internally validated in 70 patients and external validation took place in a cohort of 142 patients. Nineteen clinical variables were used for prediction in the ANN model: demographics (age), comorbidities (cardiovascular disease, chronic obstructive pulmonary disease, chronic renal failure, diabetes mellitus, dementia), medical history (colonic diverticulosis or its complications,

colonic arteriovenous malformation, use of NSAIDS or anticoagulants, residence in a nursing home), features at presentation (haematochezia, orthostatic symptoms), features at initial assessment (systolic blood pressure <100 mmHg, orthostatic signs) and initial laboratory findings (white-blood-cell count, packed-cell volume, platelet count, creatinine and prothrombin time).

The AUC for the ANN to predict the outcomes was high: 0.95 to predict which patients were in need for therapeutic intervention to control for the bleeding; 0.93 to predict recurrent bleeding; and 0.92 to predict in-hospital death. The accuracy of the prediction model was similar in the derivation and validation cohort (9). The confidence intervals for the AUC were not reported. This model was developed and validated in small patient cohorts. There is a high ratio of predictors versus outcomes, which might make this model prone to overfitting. The many predictor variables used in this model makes it a complicated, cumbersome and time-consuming process for physicians to implement in practice and therefore there is reluctance to acceptance of network models among physicians (9, 42). Further, this ANN model is not generalizable to all ED patients, as only admitted LGIB patients were included and analyzed.

1.9.5 Gradient boosting algorithm

In July 2015, Ayaru et al. published a retrospective study that aimed to test whether a gradient boosting algorithm was able to accurately predict clinical adverse outcomes in LGIB patients. Adverse outcomes were defined as therapeutic intervention, severe bleeding and recurrent bleeding (10). Severe bleeding was described as an ongoing or recurrent bleeding. A gradient boosting algorithm is a "*supervised machine learning algorithm, and is able to approximate the unknown functional mapping between the inputs and the outputs*" (10).

The authors studied two cohorts consisting of adult LGIB patients who presented to the ED between January 1st 2007 and December 31st 2011; an internal validation cohort consisting of 170 patients; and an external validation cohort including 130 patients. Thirty-nine variables were used, including demographics (age, gender), history (use of omeprazole, lansoprazole, NSAIDs, anticoagulants, alcoholism, smoking, nursing home resident, colorectal polyp, haemorrhoids, diverticular disease history, colonic arteriovenous malformation, syncope), comorbidities (cardiovascular disease, hypertension, stroke history, COPD, chronic renal failure, diabetes mellitus, dementia, cancer, chronic liver disease, previous GI bleed history, unstable comorbidities), initial assessment (heart rate, systolic BP, diastolic BP, erratic mental status, abdominal pain, tender abdominal exam, ongoing bleed in ED, gross blood on digital rectal exam),

and baseline bloodwork (haemoglobin, hematocrit, white blood cell count, platelet, activated partial thromboplastin time, prothrombin time, urea, creatinine). The predictive accuracies (sum of correct predictions over total predictions) for recurrent bleeding, therapeutic intervention and severe bleeding were 88%, 91% and 83% respectively (95% confidence intervals were not reported) when using the gradient boosting method, and these numbers were similar in the internal and external validation cohorts. When using multiple logistic regression, the accuracy to predict recurrent bleeding was 83%, to predict therapeutic intervention the accuracy was 87% and to predict severe bleeding was 71%.

Both the derivation and validation cohort have small sample sizes, and only patients who were admitted from the ED were included which decreases the generalizability of this algorithm to all ED patients. Furthermore, the authors do not mention if the predictors and outcomes have been collected in a blinded manner. Additionally, this algorithm is complex and time-consuming for ED physicians to use as it includes 39 variables, which might be contributing to the facto that this tool has not been adopted into clinical practice.

1.9.6 HAKA score

Chong et al. recently (2016) developed the HAKA score, consisting of **h**aemoglobin of <100 mg/dl on presentation, **a**spirin use, collapse *(**K**)* and **a**lbumin of <38 g/dl (8). Data of 410 ED LGIB patients was retrospectively collected and analyzed, and the authors used the same endpoint as Strate et al.; severe LGIB, defined as continued bleeding within the first 24 hours and/or recurrent bleeding after 24 hours of clinical stability and/or readmission to hospital with LGIB within one week. Patients were followed up for at least two years. After developing the HAKA score, the patient cohort was categorized for low-risk patients (HAKA score of 0-1) and high-risk patients (HAKA score of 2 or more).

The sensitivity for this rule was 59%, specificity was 82%, positive predictive value (PPV) was 44% and negative predictive value 88%. This study did not report 95% confidence intervals. This risk tool is easy to use by ED physicians as it includes only 4 variables. However, the sensitivity of the rule is only 59%, which is low. Further, mortality and need for intervention were not assessed as outcomes, while they are important adverse events that can influence disposition-decision making. In addition, it is expected that the majority of adverse outcomes will happen closely after the sentinel bleeding event. As the follow-up duration in this study is at least 2 years, it is difficult to make assumptions regarding whether events happening this late in the course are

related to the sentinel bleeding event, and whether it will affect the physician's decisions regarding the management during the ED index visit.

1.9.7 Need for a new decision tool

The above-mentioned decision tools have several methodological flaws: they are developed in small patient cohorts; are not generalizable to all ED patients; they only have a moderate ability to discriminate patients with a severe bleeding; or the tool is not feasible to use for clinicians. Because of these limitations, the decision tools are not adopted into clinical practice. There is therefore a need for a new decision tool to overcome these weaknesses and aid ED physicians in making evidence-based disposition decision-making.

Table 1						
	Published Validated	**Design**	**Patient cohort***	**Outcome†**	**Variables**	**Limitations**
BLEED(5)	1995 Yes (25)	Prospective	UGIB‡ and LGIB§ admitted to ICU‖	In-hospital: a) overall mortality; b) surgery to control the hemorrhage; c) rebleeding; d) units of transfused packed RBCs; e) Organ System Failure Index; f) hospital length of stay	• Ongoing bleeding • Low SBP¶ • Elevated prothrombin time • Erratic mental status • Unstable comorbid disease	• Small sample size (n=103) • Only admitted patient • Moderate AUC of 0.72
Strate et al.(6)	2003 Yes (27)	Retrospective	Admitted with LGIB§	Severe bleeding: Continued bleeding within the first 24h, and/or recurrent bleeding after 24h of clinical stability	• Heart rate ≥100/min • SBP¶ ≤115 mmHG • Syncope • Non-tender abdominal examination • Rectal bleeding in the first 4h of evaluation • Aspirin use • More than two comorbid conditions**	• Small sample size (n=252) • Only admitted patient • Mortality and need for intervention are not included in outcomes • Moderate AUC of 0.76
Velayos et al. (7)	2004 No	Prospective	ED patients admitted with LGIB§	Severe LGIB§: Ongoing bleeding or rebleeding after leaving the ED	• Initial hematocrit <35% • Abnormal vital signs • Gross blood on rectal exam	• Not validated • Small sample size of 94 patients • No AUC
Artificial Neural Network (9)	2003 Yes (9)	Prospective	Admitted with LGIB§	Intervention for control of haemorrhage; Recurrent bleeding; Death	20 clinical variables including • Demographics • Comorbidities • History • Features at presentation • Features at initial assessment • Initial laboratory findings	• Only admitted patient • Complicated and time-consuming • Poor acceptance by end-user
Gradient boosting algorithm(10)	2015 Yes (10)	Prospective	ED LGIB§ patients	Therapeutic intervention, severe bleeding and recurrent bleeding.	39 variables including • Demographics • History • Comorbidities • Initial assessment • Baseline bloods	• Small sample size (n=170) • Only admitted patient • Complex and time-consuming algorithm
HAKA score (8)	2016 No	Retrospective	ED LGIB§ patients	Severe bleeding: Continued bleeding within the first 24h (requires ≥2 units of packed red blood cells and/or a decrease in hematocrit of ≥20%), and/or recurrent bleeding after 24h of clinical stability	• Haemoglobin <100 mg/dl • Aspirin use • Collapse or dizziness • Albumin <38 g/dl	• Mortality and need for intervention are not included in outcomes • Follow-up duration of ≥2 years • Not validated

Overview of previously developed clinical decision tools for patients with LGIB with a description of the predictors, outcomes and limitations.

* Patient cohort of the derivation study
† Outcome in derivation study
§ LGIB: Lower gastrointestinal bleeding
** >2 active comorbid conditions according to the Charlson Comorbidity Index.
‖ ICU: Intensive care unit
¶ SBP: Systolic blood pressure
‡ UGIB: upper gastrointestinal bleeding

1.10 Rationale for the study

The management of ED LGIB patients can be complex as it is difficult to determine the site of the gastrointestinal bleeding and severity of the bleeding. As up to 76% of cases with LGIB resolves spontaneously (1, 6, 25, 27-29, 43), it is important to accurately identify the remainder of patients who might experience serious adverse events such as mortality, recurrent bleeding and need for intervention to control hemorrhage.

A clinical decision tool could aid emergency physicians in decisions regarding further management of LGIB patients by predicting the likelihood of experiencing these adverse outcomes. As some Canadian physicians have limited appropriate facilities to intervention in rural areas and access issues to intervention resources in urban settings, a robust decision tool that accurately predicts clinically important adverse outcomes after LGIB will especially aid these ED physicians in their management and patient disposition decisions, which will benefit patient safety. It would also aid physicians in determining which patients are safe for discharge from the ED in order to avoid unnecessary urgent endoscopies.

To date, no feasible clinical decision tool that accurately identifies ED LGIB patients who are at risk for death, recurrent bleeding, need for intervention and severe conditions requiring (ICU) admission has been developed or adopted into clinical practice. Previously developed tools that aim to risk-stratify LGIB patients have been created in small patient cohorts, are not generalizable to all LGIB patients presenting to the ED, or are not feasible to use in clinical practice and are therefore not adopted by physicians.

A clinical decision tool would be able to identify patients who are at risk for death, recurrent bleeding or in need for intervention in order to offer them timely appropriate management. This could decrease morbidity and mortality. Patients at low-risk for these adverse events could safely be discharged from the ED and followed up in outpatient clinics. This could decrease costs of hospitalization and in-patient intervention and the risk that comes along with endoscopy.

This chart review serves as a pilot study for the derivation of a clinical decision tool. This study should be followed up by a large prospective derivation study. This tool will further be validated, implemented and disseminated.

2. Goals & Objectives

2.1. Goals

The goal of this study was to develop a robust clinical decision tool to identify ED LGIB patients who are at high risk and at low risk for serious adverse events within 30 days. This health record review serves as a pilot study for the derivation of a clinical decision tool that will aid ED physicians in their management decisions regarding admission and discharge of LGIB patients, based on their risk of developing short-term adverse outcomes.

2.2 Objectives

Our specific objectives were:

1. To assess the disease burden of LGIB in an academic hospital in Canada.
2. To give an overview of previous developed clinical decision tools for risk stratification of LGIB patients.
3. To develop a new clinical decision tool to risk stratify ED LGIB patients
4. To compare different statistical methods in the development of a new decision tool.

3. Methods

3.1 Study Design

This study was a health records review conducted by reviewing charts of patients who presented to the emergency department with lower gastrointestinal bleeding.

3.2 Setting

We included patients who presented to the emergency departments of The Ottawa Hospital Civic Campus and General Campus, Ottawa, Canada. These sites are adult acute tertiary care emergency departments with approximately 170,000 visits annually, resulting in 50,000 admissions (44).

3.3 Study population

We identified potential eligible patients using primary and secondary ICD-10-CA codes, based on the most likely diagnosis during the ED index visit according to the ED physicians. We reviewed charts of ED patients who were assigned one of the following ICD-10-CA codes:

K55.20 Angiodysplasias of colon with bleeding
K62.5 Haemorrhage of anus and rectum
K64 Haemorrhoids and perianal venous thrombosis
K64.0 First degree haemorrhoids
K64.1 Second degree haemorrhoids
K64.10 Second degree haemorrhoids, uncomplicated
K64.11 Second degree haemorrhoids, complicated
K64.2 Third degree haemorrhoids
K64.20 Third degree haemorrhoids, uncomplicated
K64.21 Third degree haemorrhoids, complicated
K64.3 Fourth degree haemorrhoids
K64.30 Fourth degree haemorrhoids, uncomplicated
K64.31; Fourth degree haemorrhoids, complicated
K64.8 Other specified haemorrhoids
K64.9 Haemorrhoids, unspecified
K92.2 Gastrointestinal haemorrhages, unspecified
R19.50 Positive Faecal occult blood test

We included patients who met the following inclusion criteria, and who did not meet any exclusion criteria.

3.3.1 Inclusion criteria:

1) 18 years or older;
2) Acute lower gastrointestinal bleeding with an onset of <3 days.
   Clinically, acute LGIB is defined as:

a) Bright red blood per rectum in the past two days, as per history;
b) Bright red blood on the glove after digital rectal examination (DRE);
c) Clear red bloody stool (not black) during the ED visit, described as "frank blood", "bright red blood per rectum" or "gross blood" by the ED physician;

3) Criteria 2a), 2b) or 2c) should occur in patients whose primary complaint is a bleeding per rectum.

3.3.2 Exclusion criteria:

We excluded patients with the following features:

1) Evidence of upper gastrointestinal bleeding (UGIB) (e.g. coffee ground emesis, melena or hematemesis) without meeting the criteria as described in 2a, 2b or 2c;
2) Admitted with an other condition and experienced in-hospital LGIB;
3) Palliative care plan prior to the index visit.
4) LGIB due to significant trauma requiring admission;
5) Reside outside the Ottawa region, based on postal code
6) Transferred from another facility to The Ottawa Hospital

We excluded patients who solely presented with signs of an UGIB, without any symptoms suggesting LGIB as defined in criteria 2a), 2b) or 2c) of the inclusion criteria. Patients presenting with both symptoms of UGIB and LGIB were included, as the source of the bleeding could potentially be from the lower gastrointestinal tract.

Patients who received palliative care prior to the index visit and patients who previously refused further treatment for LGIB were excluded because these patients will be managed differently than patients who do not receive palliative care as their treatment is mainly focused on comfort rather than cure. Patients who decided to discontinue treatment for LGIB after initiating treatment were included in the study.

Further, we excluded patients who suffered from LGIB due to significant trauma requiring admission. Significant trauma was defined as trauma resulting in LGIB, for example injury to the pelvis. These patients are at higher risk of experiencing an outcome due to the sustained trauma, and ED physicians do not need a risk tool to guide them in their disposition decision.

We excluded patients who did not reside in the Ottawa region in order to optimize accuracy regarding identifying adverse outcomes. "Ottawa region" was determined based on postal code. Patients with a postal code starting with K1, K2 or K3 were included and patients with any other postal code were excluded. We used this approach as we expected that patients residing in Ottawa were likely to return

to a hospital in Ottawa in case an adverse event would occur. Accordingly, we expected that non-Ottawa patients were more likely to present to a hospital outside of Ottawa, which would not be feasible to track down given the scope of this study. By only including residents from Ottawa and by collecting data from all adult hospitals in Ottawa, we expected to optimize our ability to collect data on adverse outcomes.

3.4 Study Period

We reviewed charts from patients who presented to the ED between August 26th 2013 and June 30th 2014.

3.5 Data Collection

We screened charts of patients with ED diagnosis based on ICD-10-CA codes as stated in section 3.3. We collected predictor variables and outcomes of eligible patients using Case Record Forms (CRF). The CRF was developed based on CRFs that were developed for previous studies within the department. Data of 30 patients was collected after which we made adjustments to the CRF, and applied these changes to the first 30 patients. Please find the Case Record Form in the appendix.

3.5.1 Predictor variables

We extracted predictors that previous literature identified as useful for predicting which patients with LGIB are in need for further monitoring or treatment (5-7, 9, 10, 24, 45, 46). Further, we obtained predictors that are useful in risk-stratification of patients with UGIB, as identified in previous studies (47-49).

We collected the following variables:

3.5.1.1 Variables from history

- **Age** (6, 7, 9, 10, 24)
- **Sex** (9, 10, 24)
- **Presenting symptoms**:
    - Bright red blood per rectum (BRBPR)
        - Number of days with BRBPR
        - Was there BRBPR in the last 24 hours?

- Melena: reported by the patient and document in the ED chart as "melena", "tarry stool" or "black stool", along with BRBPR.
- Abdominal pain (5, 7, 10): abdominal pain (occurring with the BRBPR or in the ED) reported by the patient and documented in the ED chart.
- Syncope (6, 10): Transient global cerebral hypoperfusion that leads to a transient loss of consciousness that is rapid in onset, is short of duration and recovers spontaneously (50); along with the rectal bleeding.
- Light-headedness (6): dizziness, feeling of fainting or pre-syncope as documented in the chart of the index ED visit; along with the rectal bleeding.
- Chest pain: reported by the patient and documented in the ED chart; along with the rectal bleeding.
- Shortness of breath: reported by the patient and documented in the ED chart; along with the rectal bleeding.
- Change in bowel movement: Diarrhea or constipation along with rectal bleeding. Different than baseline.

- **Medical history and comorbidities**:
  - Diverticulosis: Reported in previous (endoscopy) reports or per history.
  - Arteriovenous malformations: Reported in previous (endoscopy) reports or per history.
  - Colorectal polyps: Reported in previous (endoscopy) reports or per history.
  - Haemorrhoids: Reported in previous (endoscopy) reports or per history.
  - Peptic ulcer disease: Reported in previous (endoscopy) reports or per history.
  - Gastrointestinal bleeding: Reported in previous (endoscopy) reports or per history.
    - Date of last episode.
  - Inflammatory bowel disease (IBD): reported by gastroenterologist or per history.
    - Crohn's disease
    - Ulcerative colitis
  - Coronary artery disease: Previous documented myocardial infarction, coronary artery bypass grafting (CABG) or angiogram confirming significant stenosis or as reported by the patient and the patient is on treatment
  - Congestive heart failure: as previously diagnosed by specialist or per history.
  - Hypertension: use of antihypertensive medication to lower the blood pressure.
  - Arrhythmia: as previously diagnosed by a cardiologist or per history.

    - Atrial fibrillation
    - Atrial flutter
  - Cerebrovascular disease: Previously diagnosed by a neurologist (or another consultant) or per history.
    - Ischemic stroke
    - Transient ischemic attack (TIA)
  - Chronic obstructive pulmonary disease (COPD): FEV1/FVC <70% during spirometry and bronchodilators ± corticosteroids ± oxygen as management, or per history.
  - Asthma: as reported in patient charts or per history.
  - Currently on dialysis: as reported in patient charts or per history.
  - Last documented creatinine in The Ottawa Hospital records (umol/L)
  - Diabetes mellitus using medication to control glucose levels.
  - Dementia as per history.
  - Malignant tumour as per history.
    - Primary tumour (colon vs. other origin)
    - Metastasis
    - Lymphoma
  - Liver disease
    - Cirrhosis: diagnosed by a specialist, based on biopsy of the liver or other imaging techniques (CT scan, MRI) or per history.
    - Portal hypertension: Documented in previously endoscopy reports as oesophageal varices or oesophageal variceal bleeding or per history.
  - Depression: Treatment with antidepressants for depression.
  - HIV or AIDS as per history.
  - First degree family history of gastrointestinal cancer
    - Upper gastrointestinal origin
    - Lower gastrointestinal origin
- **Medication use**:
  - Aspirin (5, 6, 24, 46)
  - NSAIDs (5, 9, 10, 24)

- Anticoagulation medication (5, 9, 10, 46): vitamin K antagonists (e.g. warfarin) or direct oral anticoagulants (DOACs) (e.g. Dabigatan, Argatroban, Desirudin, Bivalirudin, Rivaroxaban, Apixaban, Edoxaban) (51).
- Antiplatelets other than aspirin (clopidogrel, prasugrel, ticagrelor)
- Proton pump inhibitors (PPIs) use (10).

  A patient is positive for aspirin use if they took daily aspirin regardless of the dose in the week prior to presenting to the ED. A patient is positive for NSAID use, anticoagulant drug use and PPI use if they used 2 or more doses in the week prior to presenting to the ED (6).

  We analyzed anticoagulants and antiplatelets (except aspirin) together as "bloodthinning medication", as they both have the effect to increase bleeding time.

- **Lifestyle factors**:
  - Alcoholism: Alcoholism was identified as a potential predictor for adverse outcomes in LGIB patients (10). This variable was not further analyzed as we found, during data collection, that alcohol use was often not reliably documented.
  - Smoking status: Non-smoker, current smoker or ex-smoker (10).
  - Nursing home resident: resident of a nursing home, not of a retirement home (9).

3.5.1.2 Variables from physical examination

- Systolic and diastolic blood pressure (in mmHg) at triage, lowest value at the ED, highest value in the ED and prior to leaving the ED (5-7, 9, 45, 46)
- Heart rate (beats per minute) at triage, lowest value at the ED, highest value in the ED and prior to leaving the ED (6, 7, 9)
- Oxygen saturation (%) at triage.
- Glasgow Coma Scale (GCS) ((52) see table 2) at triage, represents an "erratic mental status" (5, 10)
- Bright red blood on digital rectal examination (6, 7): as documented by the ED physician in the chart.
- Ongoing bleed in ED (10): Red bloody stool during ED visit.
- Tender abdominal exam (10): as documented by the ED physician in the chart.

3.5.1.3 Laboratory values

Initial laboratory results obtained during the index visit.

- Haemoglobin (Hb) in g/L (46)

- Hematocrit (Hct) in L/L (7)
- Platelets $x10^9$/L (9)
- International normalized ratio (INR) (5, 9)
- Partial thromboplastin time (PTT) (9)
- White blood cell count $x10^9$/L (9)
- Creatinine in μmol/L (9)
- Blood urea nitrogen (BUN) in mmol/L (9)
- Bilirubin in μmol/L (5)
- Albumin in g/L (5)

Table 2

Feature	Components	Score
Eye opening response	Spontaneous	4
	To speech	3
	To Pain	2
	None	1
Verbal response	Orientated	5
	Confused	4
	Words (inappropriate)	3
	Incomprehensible sounds	2
	None	1
Motor Response	Obeying commands	6
	Localising pain	5
	Normal flexion (withdrawal)	4
	Abnormal Flexion	3
	Extension	2
	None	1

Glasgow Coma Scale: used in order to assess the level of consciousness. The patient is assigned a score (3-15) based on its response to (52)

3.5.1.4 Disposition Decision

We collected data regarding ED disposition including referral to consultants, discharge from ED and admission of patients.

3.6 Outcome Measures

The primary outcome was a composite outcome, consisting of all-cause mortality, rebleeding, need for intervention, and serious conditions resulting in admission due to LGIB, all within 30 days of the index visit to the ED.

We chose a composite outcome, in contrast to individual outcomes, as patients who are at risk of experiencing one of these outcomes might benefit from early care and therefore the components of the composite outcome are all of clinical importance. Previous studies on risk stratification in LGIB also use a composite outcome to identify patients at risk of adverse outcomes after LGIB.

We chose outcomes within 30 days after ED discharge based on the available follow-up time with gastroenterologists. In many centers across Canada, follow-up with gastroenterologists within 7 days will not be feasible, hence we chose 30 day outcomes rather than a shorter period of follow-up for outcome assessment. We differentiated between adverse events occurring during the index ED visit and after ED discharge, and only adverse outcomes that occurred after ED discharge were used to derive the final model. We chose this approach as ED physicians do not need a prediction tool to guide them in the management of patients who experience an adverse event in the ED, as these patients are likely to receive immediate treatment and are likely to be admitted. More so, ED physicians will benefit from a tool that predicts the risk of developing an adverse event after discharge from the ED to guide them in disposition decision-making.

3.6.1 Definitions of outcomes

Mortality: Mortality is defined as in-hospital or out-of-hospital death due to any cause. We used all-cause death in contrast to specific causes of death, as studies have shown that it can be difficult to determine exact cause of death. After a patient passes away, it is the physician's responsibility to document the cause of death and mechanism of death on the death certificate. Many studies use this information to determine the cause of death. However, the cause of death filled in on the death certificate is often inaccurate and the actual diagnosis is often missed (53, 54). Physicians who fill out the death certificate and determine the cause of death are often unfamiliar with patient's long-term medical issues and comorbid illnesses, and they might not be trained to fill out death certificates properly. Further, physicians might confuse the underlying cause of death with mechanism of death. Autopsy would give a more precise cause of death, however the results are only available after the physician filled out the death certificate, and autopsy rates are low (53-55). In order to avoid the

uncertainty regarding the precise cause of death, we used death by any cause as one of the components of our endpoint.

Recurrent bleeding: Recurrent LGIB is a significant rebleeding after 24 hours of clinical stability (stable BP, heart rate, no ongoing bleeding), further defined as hematochezia or a bleed that was found objectively during endoscopy, or when a patient presented with a clear red bloody stool or bright red blood on the glove with DRE during a ED visit following the index visit. This clinical rebleeding should be accompanied by a decrease in haemoglobin concentration of at least 20 g/L and/or additional packed red blood cell transfusions after initial successful treatment, and/or readmission for LGIB within 30 days of the index bleeding (27, 56).

Need for intervention: Need for intervention is defined as receiving any of blood transfusions, or undergoing endoscopic, angiographic embolization or surgical intervention in order to stop the bleeding after the ED visit. Endoscopy, angiographic embolization or surgery that was done to obtain further information regarding the source or aetiology of the bleeding without any intervention taking place, was not considered as an adverse outcome.

Morbidity resulting in admission due to LGIB: We also included the following conditions as an adverse event: ICU admission for LGIB related conditions; shock needing vasopressors to stabilize the patient; acute renal failure or acute on chronic renal failure/starting on dialysis; respiratory failure needing endotracheal intubation or mechanical ventilation to stabilize and maintain the airway.

3.7 Outcome assessment

3.7.1. Collecting data

Adverse events must have occurred within 30 days of the index ED visit. We followed up on patients who were admitted to the hospital as well as on patients who were discharged home.

Mortality: We checked hospital records of all adult acute care hospitals in the city of Ottawa (The Ottawa Hospital and Queensway-Carleton Hospital) to evaluate if people visited the hospital within or after 30 days after the index visit. If a patient visited one of these hospitals after 30 days, we assumed that the patient was still alive 30 days after the index visit. If we were unable to obtain information

regarding mortality from the hospital records, we reviewed the Coroner's Office for matching records for the patient.

Recurrent bleeding, need for intervention and conditions resulting in admission due to LGIB: We reviewed the hospital records of the same adult hospitals as described above. As we only included residents from Ottawa, we expected that patients returned to a hospital in Ottawa when an adverse outcome occurred.

Some patients were referred to an outpatient endoscopic clinic, not affiliated with The Ottawa Hospital. We contacted these clinics in Ottawa, and most of the clinics confirmed to have a very small number of referrals from The Ottawa Hospital (<10 patients per year) or only opened after the inclusion date of our study. However, the Star Endoscopy Ottawa clinic confirmed that they received referrals from The Ottawa Hospital and agreed to give access to endoscopy reports of patients who are included in the study and who received an endoscopy at this clinic within 30 days after the index visit. This clinic only provided us with the endoscopy reports of patients who were seen within 30 days, and did not have any other role in the study (e.g. patient enrollment, data collection, data analysis or reporting of results). Having access to patient records from this clinic, as well as from the Queensway-Carleton Hospital increased the accuracy of this outcome assessment.

Obtaining data regarding outcomes

Once we confirmed which patients were lost-to-follow up at 30 days after the index visit from The Ottawa Hospital, the candidate (RR) visited the Queensway-Carleton Hospital, the Coroner's Office and the Star Endoscopy Ottawa clinic in person with a list containing name and date of birth in order to assess if any adverse outcomes occurred. Only RR had access to this list and obtained the information regarding the outcomes in person. After data at these sites was collected, the list with patient identifying information was destroyed at The Ottawa Hospital.

3.7.2 Inter-observer Assessment

To minimize bias, two reviewers independently collected data. One reviewer collected predictors, and one second trained Research Assistant collected predictors for 10% of included patients to assess inter-observer assessment for collection of variables. We calculated the kappa value with 95% confidence intervals (CIs) for all the categorical variables that were analyzed in the univariate analysis (57). Kappa values that were 0.60 or higher were considered for inclusion in the multivariable analysis. We

did not calculate a kappa value for continuous variables, as this was age, vital signs and laboratory values which are prone to only abstraction errors and not interpretation errors.

3.7.3 Data entry and verification

A professional at the Ottawa Hospital Research Institute created a Statistical Analysis System (SAS) software database, and a data-entry professional at this institution entered data regarding the predictor variables and adverse outcomes in the database based on the Case Record Forms. The database had built-in range checks for data entry. We checked for outliers with descriptive analysis, boxplots, and by assessing the five highest and lowest values.

3.8 Data storage

We used Case Record Forms for collecting predictor variables and outcomes. We documented the subject number, date of visit, 30-day cut-off date and month and year of birth on these forms. Further, we collected the predictor variables and outcomes as mentioned in section 3.5 and 3.6. The Case Record Forms were saved in locked cabinets in The Ottawa Hospital.

A Master List contained the subject numbers, names, dates of birth, Medical Record Numbers (MRN) and date of ED index visits. This list was stored on a password protected hospital server at The Ottawa Hospital.

Only people who were directly involved in the study (research assistants, supervisor and co-supervisor, data-entry worker) had access to the Case Record Forms and the Master List. The Ottawa Hospital Research Institute and the Ottawa Health Science Network Research Ethics Board were also able to access the data collected for this study, for audit purposes.

3.9 Sample Size

The sample size that is needed for the derivation of the decision tool was based on the following equation (58):

$$N = 16 \times SN \times \frac{(1 - SN)}{\beta^2}$$

Where:

SN is the sensitivity

β is the bound of the error of estimation

The main goal of the decision tool was to correctly identify patients who are at high risk for developing an outcome after LGIB, and therefore we needed a high sensitivity and a high specificity. In order to calculate the sample size, we used a sensitivity of 95%, a bound of error of estimation between 4%-5%, and a β of 0.045.

$$N = 16 \times 0.95 \times \frac{(1 - 0.95)}{0.045^2}$$

$$N = 375.3$$

We would need a sample size of 376 patients in order to derive our clinical decision tool.

3.10 Data Analysis

3.10.1 Descriptive analysis

In order to give a complete overview of the distribution of all collected variables, we conducted a descriptive analysis. We calculated the mean with standard deviation (SD) for all the continuous variables with normal distribution and used the median with interquartile range (IQR) for continuous variables with skewed distribution. Normal distribution was determined by assessing histograms, comparing means and medians and assessing skewness. We calculated percentage with 95% CIs for binary variables.

3.10.2 Exclusion of variables

Prior to the univariate analysis, we excluded variables which:

1) Had a missing rate of >25% and were clinically less relevant. However, we assumed that patients did not have a medical comorbidity if this was not document anywhere in their records, instead of documenting this as missing data.

   INR had >25% missing data but was thought to be clinical relevant. INR is mainly affected by anticoagulants. Therefore, we imputed missing data for INR based on the assumption that people who did not take anticoagulants and did not have an INR measured would have an INR <2.0; and patients who did take anticoagulants and did not have an INR measured would have an INR of ≥2.0.
2) Had a cell count of ≤5 in the univariate analysis.

3.10.3 Univariate analysis

We analyzed our data with univariate analyses in order to evaluate the strength of association between each predictor variable and the composite outcome of death, recurrent bleeding and need for intervention to stop the bleeding. Using Statistical Analysis System (SAS) software version 9.4 and SAS University Edition, we used the independent two-tailed t-test to evaluate the strength of association between the continuous predictors (mean) and composite outcome and used the Wilcoxon Rank Sum test when we used median instead of means. The Chi-Square test was used for nominal data. Predictors with a p-value of ≤ 0.20 were considered for multivariable analyses.

3.10.4 Dichotomous variables

We dichotomized all continuous variables that were not excluded for the above-mentioned reasons. The cut-off scores were chosen on clinical relevance and statistical significance. For example, we assessed the statistical significance of multiple clinical relevant cut-offs for age and eventually chose a cut-off of 75 years. We are aware that this will cause a loss in information, however it is more feasible to use in clinical practice.

3.10.5 Multiple imputation

After dichotomizing the continuous data, we used multiple imputations to account for missing data for variables with <25 missing data. We created 10 datasets.

3.10.6 Collinearity

We tested for collinearity between predictors that were chosen after excluding for missing data, low cell count and after univariate analysis. Once collinearity was identified, we considered clinical and statistical significance. Clinical significance was based on the predictors' relevance and the reliability of retrieving the variable in a retrospective manner. Statistical significance was based on the odds ratio of predictors that showed to have collinearity in relation to the outcome. The choice for predictor selection after testing for collinearity is explained in the discussion.

3.10.7 Derivation of the model

In order to determine our final model, we applied logistic regression and recursive partitioning on the 18 predictors that were selected after descriptive analysis and univariate analysis. We are aware that

ideally you want to start your multivariable regression analysis with a limited amount of predictor variables in order to prevent overfitting. According to Harrell et al, you can determine the amount of variables at the start of a multivariable regression analysis by dividing the number of outcomes by 10 (59, 60). However, in light of this pilot study we chose a larger number of predictors.
We ran 3 different statistical methods on the 10 datasets of the multiple imputation database: SELECTION=SCORE option, stepwise backwards selection and recursive partitioning.

3.10.7.1 Stepwise backwards selection

We chose a p-value of <0.01 in order to select predictor variables for our final model. We chose a p-value of 0.01 in stead of the more commonly seen 0.05 in order to reduce the final number of predictors included in our model.

3.10.7.2 SELECTION=SCORE option

The SELECTION=SCORE option is a function in SAS to select the best subsets of covariates from a candidate set for a given model size, where the best subsets are those with the highest score chi-square statistics (61). One can manually enter the amount of desired predictors. We chose our desired amount of predictors based on the number of outcomes we had, and wanted the amount of predictors to be 10% of the number of outcomes. We used this option on all the datasets of our multiple imputation database.

3.10.7.3 Recursive partitioning

We used KnowledgeSEEKER (version 8.7) software to conduct recursive partitioning. This is a modelling technique that divides patients into smaller sub-samples based on risk factors. This leads to creating a subpopulation that includes patients with a certain outcome (37).

3.10.8 Diagnostic accuracy

We calculated the odds ratios with 95% CIs, the co-efficients for the predictors in the model, the c-statistic and the Homer-Lemeshow goodness of fit per dataset of the multiple imputation database (10 datasets).
We then combined the estimates of the logistic regression model of the 10 datasets derived with the multiple imputations to develop our final model. In order to do so, we used the Rubin's Rules. Rubin's rules allow you to combine individual estimates and standard errors from the multiple imputation datasets in order to provide valid statistical results. One can apply the Rubin's rules to a fitted

prognostic model, which performance is evaluated within each imputed dataset, after appropriate transformations to improve normality (62).

We applied the final selected predictor variables to our original database, and calculated the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR-) with 95% CIs.

3.10.9 Comparison of the two modelling techniques

While we anticipated that logistic regression would be the preferred multivariable analysis, we chose to also conduct multivariable analysis using recursive partitioning. This modelling technique is commonly used when deriving clinical decision rules where near perfect sensitivity is desirable. Logistic regression analyses often leads to decision rules with a higher specificity but less than optimal sensitivity (37, 63).

3.11 Characteristics of LGIB patients presenting to the ED in Ottawa

We reported a description of the characteristics of ED patients presenting with LGIB. The mean and standard deviation or the median and interquartile range were calculated for the following characteristics:

- Burden of LGIB on the ED: Patients presenting with LGIB as a proportion of all ED visits.
- Proportion of hospitalized patients: Percentage of patients with LGIB presenting to the ED who are admitted after ED discharge;
- Proportion of patients who develop an adverse event in the ED, and the percentage of patients who experience this outside of the ED.

3.12 Ethical approval

The Ottawa Health Science Network Research Ethics Board (OHSN-REB) approved the study protocol prior to initiating the study. Because we followed up on patients in the Queensway-Carleton Hospital, the REB of this hospital also approved the study. The Coroners Office and Star Endoscopy Ottawa clinic signed an agreement with The Ottawa Hospital regarding the study. All institutions approved the protocol with waiver of consent requirement from study patients.

Included patients are not at increased risk of harm by being included in the study as this is a retrospective study and the LGIB, treatment and potential adverse events had already occured at the time we started this study. Participating in this study did not change their management. We did not contact patients and thus patients did not sign an informed consent form.

Patients were assigned a subject number, which was recorded on the Case Record Form. The Case Record Forms did not contain any personal identifying information. The Case Record Forms were saved in a locked cabinet at The Ottawa Hospital. The Master List also contained the subject number in order for us to track patients down. This list did contain personal identifying information and was saved on a password protected server of The Ottawa Hospital, and was only accessible to people directly involved in the study.

The copies of the REB approvals and agreements are attached in the appendix.

4. Results

4.1 Patient selection

Please see figure 1 for an overview of patient selection. A more detailed explanation will follow below.

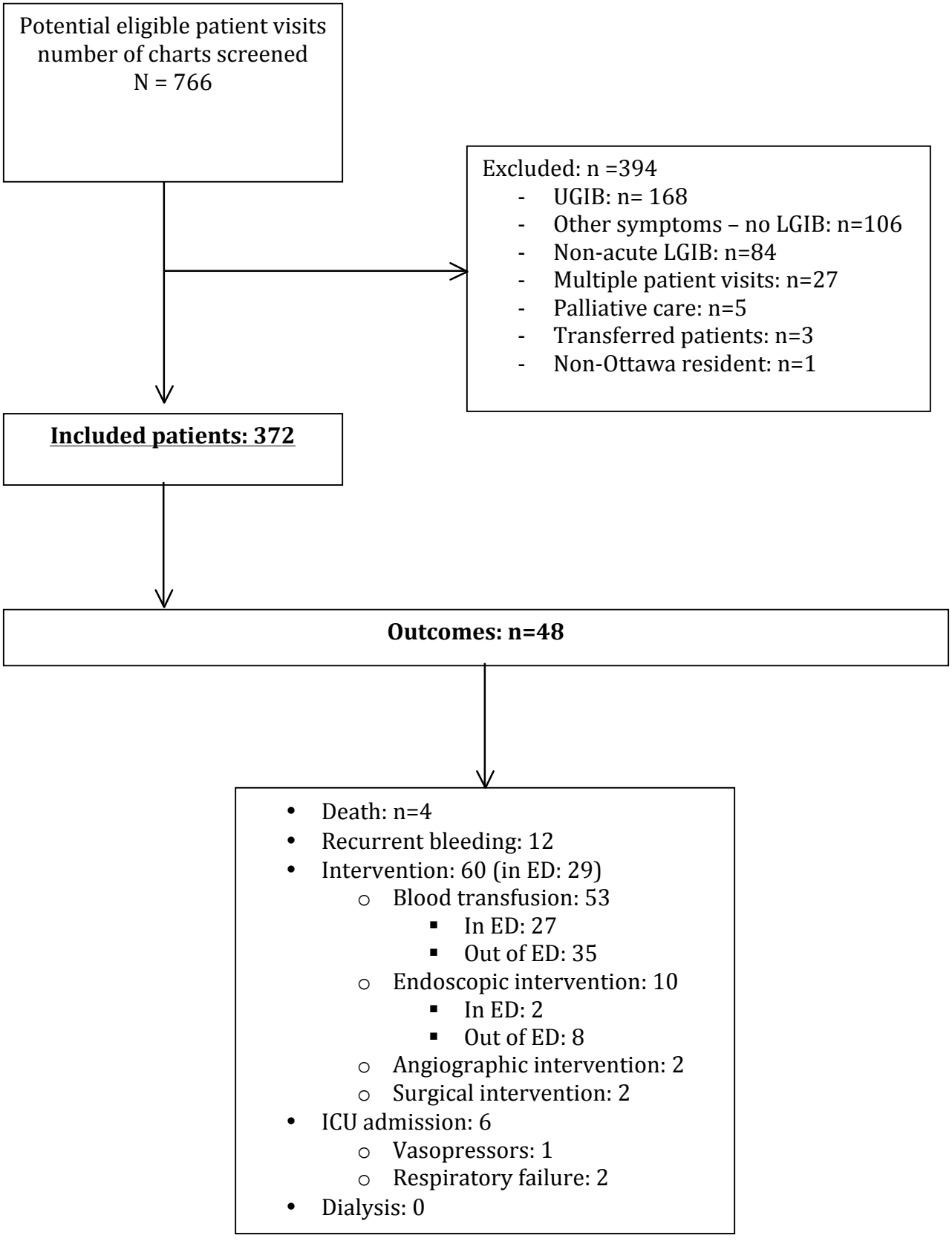
We identified 766 potential eligible patient visits to the emergency departments of The Ottawa Hospitals with an ICD-10-CA code as specified in section 3.3. We excluded 394 visits for the following reasons:

- 168 patients had an upper gastrointestinal bleeding rather than a lower gastrointestinal bleeding and were therefore excluded.
- 106 patients presented with other symptoms than specified under section 3.3.1 (e.g. rectal pain, epistaxis, fatigue, syncope etc.).
- 84 patients presented with a non-acute LGIB: they had no bleeding in the last 24 hours and the last bleed was reported >2 days prior to ED presentation.
- 27 patient visits were excluded, as these patients had repeated visits to the ED for LGIB during the study period. Only the first eligible patient visit was included.
- 5 patients received palliative care prior to presenting with LGIB to the ED.
- 3 patients were transferred to The Ottawa Hospital from other facilities.
- 1 patient was a non-Ottawa resident.

We initially planned to exclude patients whose sentinel bleed was an in-hospital bleed and patients who suffered a LGIB due to a trauma. We did not identify any patients meeting these criteria.

In total, we included 372 patients in our study.

Figure 1: flow diagram of patient selection



4.2 Patient characteristics

4.2.1. Epidemiology of LGIB patients presenting to the Emergency Department

In 2014, 159,916 patients presented to the Emergency Departments of the Civic and General campus of The Ottawa Hospital. In that year, 1,226 (0.8%) presented with a lower gastrointestinal bleed.

4.2.2 Demographics and past medical history

A summary of the baseline demographic characteristics and medical history of the 372 patients who were included in the study is provided in table 3.

The mean age was 62.3 years (SD 22.5) and approximately half of the patients were male (53.4%). Almost 10% of patients were nursing home residents. Seventeen percent of the 182 patients for who this was documented, had a family member who was diagnosed with cancer in the gastrointestinal tract. For 47.4% of the patients it was reported that they were current or former smokers.

Eighty-one patients (21.8%) experienced a lower or upper gastrointestinal bleeding at any time prior to the sentinel bleed. Almost a quarter of the patients had a past medical history of haemorrhoids (23.1%), 16.7% had a history of diverticulosis and 16.1% was previously diagnosed with colorectal polyps.

More than half of the patients suffered from one or more cardiovascular related conditions (55.4%). Fifty-nine patients (15.9%) were diagnosed with coronary artery disease; 10.8% of patients had a prior myocardial infarction and 5.1% had angina. Further, 43.8% of patients were treated for hypertension, 17.7% were treated for diabetes mellitus, 14.3% had atrial fibrillation and only 1 patient was diagnosed with atrial flutter. Forty-three patients (11.6%) ever suffered from a cerebrovascular disease.

Twenty-two (5.9%) and 16 (4.3%) patients suffered from COPD or asthma, respectively. For 10.5% of the patients it was reported that they had dementia at the time of their emergency department visit. Just over two percent (2.4%) of patients were diagnosed with liver cirrhosis and 11.6% was diagnosed with depression and using antidepressant medication.

Table 3	
Characteristic (n of patients in analysis)	**Total sample size: n=372 (%)**
Demographics (total sample size: n=372)	
Age in years, mean (SD[a])	62.3 (22.5)
Male	198 (53.4)
Nursing home resident (N=370)	35 (9.5)
Family history of cancer of the gastrointestinal tract (n=182)	31 (17.0)
Smokers (n=266) • Former smoker • Current smoker • Unknown	126 (47.4) • 82 (30.8) • 42 (15.8) • 2 (0.8)
Medical history (n=372)	
Previous gastrointestinal bleeding	81 (21.8)
Haemorrhoids	86 (23.1)
Diverticulosis	62 (16.7)
Colorectal polyps	60 (16.1)
Arteriovenous malformation	3 (0.8)
Peptic ulcer disease	13 (3.5)
Inflammatory Bowel Disease • Crohn's disease • Ulcerative colitis	8 (2.2) • 4 (1.1) • 4 (1.1)
Having ≥1 cardiovascular related conditions	206 (55.4)
Coronary artery disease • Myocardial infarction • Angina	59 (15.9) • 40 (10.8) • 19 (5.1)
Hypertension	163 (43.8)
Diabetes Mellitus	66 (17.7)
Atrial fibrillation	53 (14.3)
Atrial flutter	1 (0.3)
Congestive heart failure	31 (8.3)
Cerebrovascular disease • Cerebrovascular accident • Transient ischemic attack	43 (11.6) • 23 (6.2) • 21 (5.6)
Chronic obstructive pulmonary disease	22 (5.9)
Asthma	16 (4.3)
Currently on dialysis	10 (2.7)
Dementia	39 (10.5)
Malignant tumor • Metastasis from any malignancy • Colon cancer	71 (19.1) • 14 (19.7) • 13 (18.3)
Lymphoma	4 (1.1)
Liver disease • Cirrhosis • Portal hypertension	9 (2.4) • 9 (2.4) • 8 (2.2)
Human immunodeficiency virus/Acquired immune deficiency syndrome (HIV/AIDS)	0 (0)
Depression	43 (11.6)

Demographics and past medical history of the total patient cohort.
The exact number of patients analyzed was specified after the variable.
[a] SD = Standard deviation

4.2.3 Medication use

An overview of the medication used by the included patients is given in table 4. Just over a quarter of the patients had used aspirin in the week prior to their index ED visit (25.5%). In total, 12.9% of all patients were on an anticoagulant: 8.1% of patients was on a vitamin K antagonist and 4.8% of patients used a DOAC. Twenty patients (5.4%) used antiplatelets other than aspirin. Almost a quarter of the patients (24.1%) used a proton pump inhibitor prior to the ED visit, and 6% of patients used NSAIDs.

Table 4	
Medication group	**Patients n=369 (%)**
Aspirin	94 (25.5)
Non-steroidal anti-inflammatory drugs	22 (6.0)
Anticoagulants • Vitamin K antagonist • Direct Oral Anticoagulants	48 (12.9) • 30 (8.1) • 18 (4.8)
Antiplatelets	20 (5.4)
Proton pump inhibitors	89 (24.1)

Summary of medication use of included patients.

4.2.4 Symptoms and physical examination

In table 5, an overview of the symptoms and physical examination related to the ED index visit is provided. More than a third of the patients experienced abdominal pain during an episode of BRBPR or while they were in the ED (35.0%) and 27.1% of the patients had a tender abdomen during physical exam. A quarter of the patients felt light-headed or dizzy during their BRBPR episode or in the ED (25.4%), but only 3.1% of all patients experienced a syncopal episode prior to their ED visit. For 25% of the patients it was not documented if they experienced chest pain, and for 32.5% of patient it was not documented whether or not they were short of breath. The rate of occurrence of these symptoms was <10% in the patients for whom this was recorded on the chart. Five percent of patients presented with melena (as per history) along with bright red blood per rectum.

In 49.0% of the patients, the ED physician had blood on the glove during digital rectal examination, and 12.4% had a documented clear red bloody stool during their ED visit.

Table 5	
Characteristics	**Patients n (%)**
Symptoms	
Abdominal pain (n=329)	115 (35.0)
Light-headedness (n=307)	78 (25.4)
Syncope (n=292)	9 (3.1)
Chest pain (n=279)	5 (1.8)
Shortness of breath (n=251)	19 (7.6)
Melena (n=372)	19 (5.1)
Physical examination	
Positive digital rectal examination (n=317)	155 (49.0)
Clear red bloody stool in the Emergency Department (n=362)	45 (12.4)
Tender abdominal examination (n=328)	89 (27.1)

Summary of presenting symptoms and physical examination findings as performed during the index emergency department visit.

4.2.5 Vital signs

An overview of the vital signs in the ED is provided in table 6.

At triage, the mean systolic blood pressure was 137.4 (SD 25.7), mean diastolic blood pressure was 76.4 (SD 14.2) and mean heart rate was 83.9 (SD 18.8). Further, the mean oxygen saturation was 97.5 (SD 2.1).

Table 6				
	Triage	**Lowest**	**Highest**	**Disposition**
Mean Systolic blood pressure in mmHg (n=371)	137.4 (25.7)	127.6 (25.8)	147.4 (24.5)	138.7 (23.9)
Mean Diastolic blood pressure in mmHg (n=371)	76.4 (14.2)	69.8 (15.2)	81.6 (12.6)	75.2 (13.4)
Mean Heart rate in beats per minute (n=371)	83.9 (18.8)	75.5 (15.3)	87.6 (18.8)	78.8 (14.8)
Mean Oxygen saturation in percentage (n=335)	97.5 (2.1)			
GCS[a] n=171 median (IQR[b]) (n=172)	15 (15-15)			

Summary of blood pressure and heart rate at triage and disposition, and the lowest and highest blood pressure measured during the emergency visit stay. Oxygen saturation and Glasgow Coma Scale at triage.
Numbers are in Mean with standard deviation, and median with interquartile range for Glasgow Coma Scale.
[a] GCS = Glasgow Coma Scale
[b] IQR = Interquartile range

4.2.6 Laboratory values

The mean and median for the laboratory values are summarized in table 7. Almost eighty percent of patients had blood drawn in the ED. Among these patients, mean haemoglobin was 123 (SD 24.7), mean hematocrit was 0.367 (SD 0.067) and median creatinine was 81 (IQR 66-102). Just over half of the patients had an INR measured (53.8%), and the median INR in the total patient cohort was 1.2 (IQR 1.1-1.3). We further specified the mean INR for patients who used anticoagulants versus patients who did not. The mean INR in patients who used a vitamin K antagonist was 4.0 (SD 2.5). The mean INR in patients who used DOACs was 1.4 (SD 0.3) and for patients who did not use a vitamin K antagonist or a DOAC it was 1.2 (SD 0.5).

We believed that INR is an important possible predictor and therefore we imputed data based on the assumption that patients who did not use a vitamin K antagonist would have an INR <2 and patients who did use this type of medication would have an INR ≥2. We created two new categories for INR based on this assumption. One group consisted of patients who had an INR <2.0 and patients who did not have INR measured but did not use a vitamin K antagonist (92.2% of patients). The other group (7.8% of patients) consisted of patients whose INR was ≥2.0 and patients who did not have INR measured but did use a vitamin K antagonist.

Table 7

Laboratory values	**Median (IQR[a])**
Hemoglobin g/L (n=295)	123.0 (24.7)[a]
Hematocrit L/L (n=295)	0.367 (0.067)[a]
Platelets x10^9/L (n=295)	228 (176-284)
Creatinine µmol/L (n=285)	81 (66-102)
International normalized ratio (n=200)	1.2 (1.10-1.30)
White blood cell count x10^9/L (n=295)	8.2 (6.6-10.2)
Blood Urea Nitrogen mmol/L (n=284)	6.9 (5.1-9.8)
Bilirubin µmol/L (n=142)	7 (6-12)
Albumin g/L (n=58)	33 (31-37)

Summary of the laboratory values measured in the Emergency Department.
The median with interquartile range are reported, except for hemoglobin and hematocrit which are reported by mean and standard deviation.
[a] IQR = interquartile range

4.3 Disposition decision

A total of 28.2% patients were admitted to the hospital directly following their index ED visit. Of these patients, 74.3% were admitted to the surgical inpatient service and 24.8% were admitted to the internal medicine service. No patients were admitted to the ICU directly from the emergency department. An overview of the disposition after ED discharge is given in table 8.

Table 8	
Admitted (n=105, 28.2%)	**N (%)**
• Surgical service • General Internal Medicine service • Intensive Care Unit	• 78 (74.3%) • 26 (24.8%) • 0 (0%)

Distribution of admitted patient per service.

4.4 Adverse events

A break down of the outcomes experienced outside of the ED is provided in table 9.
In total, there were 61 adverse events. Thirteen events occurred in the ED (3.5%), while 48 (12.9%) happened after ED discharge but within 30 days of the index visit. Four patients died after ED discharge. Twelve patients experienced a recurrent bleeding after ED discharge. Furthermore, 47 interventions were needed to address the bleeding; 33 patients received blood transfusion after ED discharge; and 14 patients required intervention to stop the bleeding. Ten patients needed an endoscopic intervention; 2 patients needed a surgical intervention; and 2 patients received angiographic embolization. Six patients required ICU admission after ED discharge; one of them required vasopressors and 2 patients experienced respiratory failure. No patients required dialysis after the sentinel bleed. Some patients experienced multiple outcomes.

Table 9	
Outcome (Total cohort N=372)	**N (% of total patient cohort)**
Death	4 (1.1)
Recurrent bleeding	12 (3.2)
Need for intervention • Blood transfusion • Endoscopy • Surgery • Embolization	47 (12.1) • 33 (8.9) • 10 (2.7) • 2 (0.5) • 2 (0.5)
Intensive Care Unit admission • Respiratory failure • Vasopressors	6 (1.6) • 2 (0.5) • 1 (0.3)
Dialysis	0 (0)

Summary of outcomes experienced after ED discharge.
This table does not include the 13 events that happened during the emergency department stay.

4.5 Inter-observer Agreement

One research assistant collected data for all patients. A second research assistant collected data on 10% of the study patients (36 patients). The kappa value varied from 0.37 – 1.00, and was slightly higher among variables from the past medical history and medications compared to symptoms (0.78, 0.76 and 0.52, respectively). Table 10 displays an overview of the kappa-value per variable and per subcategory.

Table 10

		95% CI	
Variable	**Kappa**	**Lower limit**	**Upper limit**
Symptoms			
Positive DRE	0.43	0.17	0.69
Bloody stool in the ED	0.59	0.29	0.90
Abdominal pain	0.50	0.28	0.71
Dizziness	0.37	0.14	0.60
Tender abdomen on physical exam	0.49	0.22	0.76
Melena	1.00	1.00	1.00
Total	**0.52**	**0.42**	**0.63**
Past medical history			
Diverticulosis	0.93	0.79	1.00
Colorectal polyps	0.60	0.25	0.95
Hemorrhoids	0.58	0.25	0.91
Gastrointestinal bleed	0.92	0.75	1.00
Coronary artery disease	0.54	0.19	0.89
Congestive heart failure	0.79	0.38	1.00
Hypertension	0.72	0.49	0.95
Atrial fibrillation	0.82	0.59	1.00
Cerebrovascular disease	0.79	0.38	1.00
Diabetes mellitus	0.62	0.23	1.00
Dementia	0.84	0.54	1.00
Tumor	0.89	0.69	1.00
Depression	0.79	0.38	1.00
Total	**0.78**	**0.70**	**0.85**
Medication			
Aspirin	0.65	0.37	0.92
NSAIDs	0.47	-0.15	1.00
Bloodthinners	0.72	0.43	1.00
Protonpump inhibitors	1.00	1.00	1.00
Total	**0.76**	**0.62**	**0.90**

Kappa values for every binary variable included in the univariate analysis and the total kappa value with 95% confidence intervals

4.6 Exclusion of variables

4.6.1 Exclusion due of missing data

The following 9 predictors had >25% missing data and were clinically less relevant than other potential predictors. Hence, we excluded these variables:

- Symptoms: chest pain, shortness of breath, change in bowel movement (diarrhea or constipation)
- Positive family history of gastrointestinal cancer (upper gastrointestinal cancer or lower gastrointestinal cancer)
- Alcoholism, Smoking
- Triage: Glasgow Coma Scale
- Laboratory values: bilirubin, albumin

There was 46.2% data missing for INR, however we believed that this predictor is clinically important as a high INR affects the bleeding time and can therefore result in a longer duration of the bleeding and consequently a more severe bleeding, which could affect the outcome. Therefore, we imputed data for this variable as described in the methods, Section 4.2.5.

4.6.1.2. Demographics of missing data

We compared the missing data for patients with and without the outcome for the variables that were excluded for a high missing data percentage. Missing data varied from 25.0-84.4%. An overview of the comparison is provided in table 11.

For only 1 (2.8%) patient who experienced the outcome, history on chest pain was missing compared to 28.1% of the patients who did not experience the outcome ($p<0.0001$). Data shortness of breath was missing in 12.5% of patients who experienced an outcome compared to 35.5% of patients who did not experience an outcome (0.002). Change in bowel movement was not well documented in both groups (41.7% vs 47.2%, $p=0.47$). Alcohol use and smoking were missing in 10.4% of the patients who experienced an outcome versus 31.5% of patients who did not experience the outcome ($p=0.001$).

Table 11				
Variable	**Missing n (%)**	**Missing outcome (%)**	**Missing No outcome (%)**	**p-value**
Chest pain	93 (25.0)	1 (2.1)	92 (28.4)	<0.0001
Shortness of breath	121 (32.5)	6 (12.5)	115 (35.5)	0.002
Change in bowel movement	173 (46.5)	20 (41.7)	153 (47.2)	0.47
Family history of GI cancer	190 (51.1)	18 (37.5)	172 (53.1)	0.04
Alcoholism	107 (28.8)	5 (10.4)	102 (31.5)	0.002
Smoking	107 (28.8)	5 (10.4)	102 (31.5)	0.002
Glasgow Coma Scale	200 (53.8)	15 (31.3)	185 (57.1)	0.001
Bilirubin	230 (61.8)	17 (35.4)	213 (65.7)	<0.0001
Albumin	314 (84.4)	29 (60.4)	285 (87.1)	<0.0001

Rate of missing data for variables with >25% missing data per outcome group.
INR had >25% missing data but is not included in this overview as it was considered to be of more clinical significance than other variables and was therefore included in the univariate and multivariate analysis.

4.6.2. Exclusion due to of low cell count

We excluded the following 12 predictors due to a low cell count during the univariate analysis (≤5 patients for one or more cells in a Chi-square test):

- Presenting symptoms: syncope
- Past medical history: arteriovenous malformation, peptic ulcer disease, inflammatory bowel disease, COPD, asthma, currently on dialysis, metastatic cancer, colon cancer, lymphoma, liver disease, HIV/AIDS

4.7 Univariate analysis

We divided the patient cohort in two groups: patients who experienced one or more components of the composite outcome within 30 days after ED discharge (n=48) and those who did not (n=324). We performed tests of associations between individual predictors and the composite outcome. The results can be found in tables 12, 13 and 14.

4.7.1 Demographics

More males than females experienced an adverse event, however this difference was not a statistically significant (p = 0.17). Patients who experienced an outcome were older (77.5 years vs. 60.1 years, p-value <0.0001) and were more often nursing home residents compared to patients who did not experience an outcome (20.8% vs. 7.8%, p-value 0.004) (Table 12).

4.7.2 Past medical history

With regards to the medical history, patients who experienced an adverse event were also more likely to have diverticulosis (31.3% vs. 14.5%, p=0.004), colorectal polyps (35.4% vs. 13.3%, p<0.0001) and they were more likely to have experienced a gastrointestinal bleeding previously (39.6% vs. 19.1%, p=0.001). Patients who suffered from one or more cardiovascular conditions were more likely to experience the outcome (81.3% vs. 51.5%, p=0.0001) (Table 12).

4.7.3 Findings in the Emergency Department

Patients who presented with features of melena along with BRBPR more often experienced the adverse outcome compared to patients who did not reported to have melena (12.5% vs. 4.0%, p=0.013). Further, patients which were found to have blood on the glove during the DRE were more likely to experience the outcome (78.1% vs. 44.6%, p<0.0001) as well as patients who had an ongoing bleeding in the ED (30.4% vs. 9.8%, p=<0.0001) (Table 13).

4.7.4 Vital signs

Blood pressure and heart rate at triage were significantly associated with the outcome. Mean systolic blood pressure was lower in the cohort of patients who experienced an adverse event compared to the other group (128.3 mmHg vs. 138.7, p-value 0.01). The mean diastolic blood pressure was 71.6 mmHg (SD 14.7) vs. 77.2 (SD 13.9, p-value 0.01) and the mean heart rate was 91 (SD 25.3) vs. 83 (SD 17.7, p-value=0.04) (Table 13).

4.7.5 Laboratory values

The mean hemoglobin was lower in the patients who experienced an outcome compared to patients who did not (100.3 vs 127.4 g/L, p-value <0.0001). The INR was higher in the group who experienced an outcome (2.2 vs 1.4, p-value 0.001). The creatinine was higher in the outcome group (148.1 vs 94.2 μmol/L, p-value <0.0001), as was the blood urea nitrogen (12.1 vs 7.9 mmol/L, p-value <0.0001) (Table 14).

Table 12			
	Outcome occurred?		
Predictors	**No (324)** (%)	**Yes (48)** (%)	**p-value**
Demographics			
Male	168 (51.9)	30 (62.5)	0.17
Age in years, mean (SD)[a]	60.1 (22.7)	77.5 (13.9)	<0.0001
Nursing home resident	25 (7.8)	10 (20.8)	0.004
Medical history			
Gastrointestinal related			
Diverticulosis	47 (14.5)	15 (31.3)	0.004
Arteriovenous malformation	3 (0.9)	0 (0)	1
Colorectal polyps	43 (13.3)	17 (35.4)	<0.0001
Haemorrhoids	77 (23.5)	10 (20.8)	0.59
Peptic Ulcer disease	10 (3.1)	3 (6.3)	0.23
Inflammatory Bowel Disease	6 (1.9)	2 (4.2)	0.28
• Crohn's disease	• 3 (0.9)	• 1 (2.1)	1
• Ulcerative colitis	• 3 (0.9)	• 1 (2.1)	1
Previous gastrointestinal bleeding	62 (19.1)	19 (39.6)	0.001
Cardiovascular related			
Coronary artery disease	45 (13.9)	14 (29.2)	0.01
• Angina	• 15 (4.6)	• 4 (8.3)	1
• Previous myocardial infarction	• 29 (9.0)	• 11 (22.9)	0.51
Congestive heart failure	24 (7.4)	7 (14.6)	0.09
Hypertension	134 (41.4)	29 (60.4)	0.01
Atrial fibrillation	39 (12.0)	14 (29.1)	0.002
Atrial flutter	0 (0)	1 (2.1)	0.13
Cerebrovascular disease	32 (9.9)	11 (22.9)	0.01
• Cerebrovascular accident	• 19 (5.9)	• 4 (8.3)	• 0.30
• Transient ischemic attack	• 14 (4.3)	• 7 (14.6)	• 0.31
Diabetes Mellitus	49 (15.1)	17 (35.4)	0.001
Having ≥1 cardiovascular related conditions	167 (51.4)	39 (81.3)	0.0001
Other			
Chronic obstructive pulmonary disease	17 (5.3)	5 (10.4)	0.18
Asthma	14 (4.3)	2 (4.2)	1.0
Currently on dialysis	6 (1.9)	4 (8.3)	0.03
Dementia	29 (9.0)	10 (20.8)	0.01
Malignant tumor	55 (17.0)	16 (33.3)	0.01
• Colon cancer	• 11 (3.4)	• 2 (4.2)	0.72
Lymphoma	4 (1.2)	0 (0)	1
Liver disease	8 (2.5)	1 (2.1)	1
• Cirrhosis	• 8 (2.5)	• 1 (2.1)	1
• Portal Hypertension	• 7 (2.2)	• 1 (2.1)	1
HIV/AIDS	0 (0)	0 (0)	1
Depression	36 (11.1)	7 (14.6)	0.48
Family history of gastrointestinal cancer	26 (17.1)	5 (16.7)	1
Smokers	106	20 (46.5)	0.88
• Current	• 38 (11.7)	• 4 (8.3)	• 0.20
• Former	• 66 (20.4)	• 16 (33.3)	• 0.20

Table 12: Univariate analysis with demographics and past medical history.
Comparison between occurrence of predictors in the outcome cohort versus the cohort who did not experience an outcome.
* HIV/AIDS = Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome
[a] SD = standard deviation

Table 13			
	Outcome occurred?		
Predictors	**No (324)**	**Yes (48)**	**p-value**
Symptoms			
Abdominal pain	102 (35.4)	13 (31.7)	0.64
Syncope	7 (2.8)	2 (4.7)	0.63
Light-headedness	63 (24.1)	15 (32.6)	0.22
Chest pain	5 (2.2)	0 (0)	0.59
Shortness of breath	14 (6.9)	5 (11.9)	0.33
Melena	13 (4.0)	6 (12.5)	0.13
Physical examination			
Positive digital rectal examination	123 (44.6)	32 (78.1)	<0.0001
Clear red bloody stool in the Emergency Department	31 (9.8)	14 (30.4)	<0.0001
Tender abdominal examination	78 (27.6)	11 (24.4)	0.66
Vital signs, mean (SD)			
Systolic blood pressure at triage	138.7(25.5)	128.3 (25.4)	0.01
Diastolic blood pressure at triage	77.2 (13.9)	71.6 (14.7)	0.01
Heart rate at triage	83.0 (17.7)	91.0 (25.3)	0.04
Oxygen saturation at triage	97.5 (2.0)	97.5 (2.6)	0.88
Glasgow Coma Scale at triage	14.8 (0.8)	14.6 (1.4)	0.53

Univariate analysis for symptoms and physical examination during the index emergency department visit

Table 14			
	No outcome (n=247) Mean (SD)	**Outcome (n=48) Mean (SD)**	**p-value**
Hemoglobin g/L	127.4 (21.9)	100.3 (25.9)	<0.0001
Hematocrit L/L	0.378 (0.059)	0.306 (0.285)	<0.0001
Platelets $x10^9$/L	241.7 (95.7)	221.2 (140.8)	0.02
International normalized ratio	1.4 (1.1)	2.2 (2.1)	0.001
White blood cell count $x10^9$/L	8.7 (3.5)	9.3 (3.7)	0.20
Creatinine μmol/L	94.2 (83.8)	148.1 (111.1)	<0.0001
Blood Urea Nitrogen mmol/L	7.9 (7.2)	12.1 (9.8)	<0.0001

Univariate analysis of laboratory values and the outcome.
Tested with Wilcoxon Rank Sum test.

4.7.6 Medication use

All the medications we studied were significantly associated with the adverse outcome. Patients who have had an adverse event were more likely to use aspirin (p=0.016), NSAIDs (p=0.040) and proton pump inhibitors (p=0.0004). There was no significant difference between the use of antiplatelets in both groups (p=0.1581). Among the patients who experienced an outcome, more patients used anticoagulants compared to the patients who did not experience an outcome (29.2% vs 10.5%, p 0.0003) (Table 15).

Table 15			
	Outcome occurred?		
Medication group	**No (324)**	**Yes (48)**	**p-value**
Aspirin	75 (23.4)	19 (39.6)	0.016
NSAIDs [a]	16 (5.0)	6 (12.5)	0.040
Anticoagulants • Vitamin K antagonist • New Oral Anticoagulants	34 (10.5) • 18 (5.6) • 16 (4.9)	14 (29.2) • 12 (25) • 2 (4.2)	0.0003
Antiplatelets	15 (4.6)	5 (10.4)	0.158
Proton pump inhibitors	68 (21.1)	21 (44.7)	0.0004

Univariate analysis for medication use

[a] NSAIDs = Nonsteroidal anti-inflammatory drugs

4.7.7 Predictors for multivariable analysis

As mentioned before, we excluded predictor variables with a high (>25%) missing data rate, a low (<5) cell count, and variables with a p-value of >0.20 with univariate analysis. We also included clinical relevance and reliability (kappa value >0.60) in our final predictor selection for the multivariable analysis.

Based on these considerations, we included the following 26 variables for multivariable analysis:

Demographics: age, nursing home resident;

Presenting symptoms: melena;

Physical exam: positive DRE, clear red bloody stool in ED

Vital signs: SBP, DBP and heart rate at triage, SBP and DBP at discharge, and highest HR during the ED stay.

Medical history: diverticulosis, colorectal polyps, previous gastrointestinal bleeding, cardiovascular related disease, malignant tumour, dementia;

Medication: aspirin, NSAIDS, blood thinning medication, proton pump inhibitors;

Laboratory values: INR, hemoglobin, hematocrit, creatinine, BUN.

4.8 Collinearity and predictor selection

We tested these 26 clinically and statistically significant variables for collinearity. When we detected collinearity between two predictor variables, we looked at clinical relevance, reliability and statistical significance of both predictor variables in order to make a decision on which one to exclude from further analysis. An overview of the odds ratio's (ORs) of the predictors with collinearity with the outcome is given in table 16. We will explain the selected predictors further in the discussion.

Collinearity between age and cardiovascular condition

There was collinearity between "having one or more cardiovascular related condition" and "age over 75 years". Both of the predictors were similarly associated with the outcome (OR age 3.95, 95% CI 3.22-4.83; OR for cardiovascular comorbidity 4.07, 95% CI 3.21-5.18). We reasoned that "having one or more cardiovascular related condition" was less accurate than "age over 75 years", as the former one consists of multiple conditions and information was retrieved in a retrospective matter. Therefore, we used "age over 75" in our multivariable regression model.

Collinearity between heart rate at triage and highest heart rate

There was also collinearity found between the "heart rate measured at triage" and the "highest heart rate measured during the ED visit". The OR for "heart rate at triage" for experiencing the adverse event was 2.44 (95% CI 1.98-3.02) while the OR for the "highest heart rate measured in the ED" was 2.74 (95% CI 2.24-3.35). The highest heart rate measured in the ED if often influenced by the moment the heart rate is measured and the frequency that the heart rate is measured which makes this a more subjective variable than heart rate measured at triage. Therefore, we used the "heart rate at triage" in our multivariable regression analysis.

Collinearity between diastolic blood pressure at triage and disposition

Diastolic blood pressure at triage and at disposition from the ED showed to have collinearity. They were equally associated with the outcome (DBP at triage: OR 2.66, 95% CI 2.19-3.23; DBP at disposition: OR 2.66, 95% CI 2.19-3.23). We considered DBP at triage in the multivariable regression analysis.

Collinearity between SBP at triage and at disposition

The OR for SBP at triage was 2.06 (95% CI 1.64-2.59), while the OR for SBP at disposition was 2.62 (95% CI 2.03-3.42). We considered SBP at triage for the final predictor selection.

Collinearity between blood thinning medication and INR

Using blood thinning medication and INR measurement in the ED were similarly correlated with the outcome. The odds ratio for blood thinners for experiencing the outcome was 3.62 (95% CI 2.84-4.45) while this was 6.02 for INR (95% CI 4.65-7.91). We chose to use INR for our multivariable regression analysis.

Collinearity between haemoglobin and hematocrit

Hemoglobin and hematocrit showed to have collinearity. The OR for hemoglobin was 10.77 (95% CI 8.45-13.68); the OR for hematocrit was 12.26 (95% CI 9.88-15.21). We used hemoglobin in the multivariable regression analysis.

Collinearity between dementia and nursing home residents

There was collinearity between having dementia and living in a nursing home.

The relation between these two predictors and the outcome was equally strong (OR 2.68 for dementia and 3.09 for living in a nursing home). As having dementia was not always documented in the charts, we thought this would not be a reliable predictor to use. Therefore, we used living in a nursing home in the multivariable analysis.

Collinearity between creatinine and blood urea nitrogen

In our patient cohort, BUN (OR 5.04, 95% CI 3.92-6.48) had a stronger correlation with the outcome compared to creatinine (OR 2.49, 95% CI 2.02-3.07). We used BUN in the multivariable regression analysis.

Table 16			
		95% CI	
Predictor	**OR**	**Lower limit**	**Upper limit**
Age ≥75 years	3.95	3.22	4.83
Cardiovascular condition	4.07	3.21	5.18
Heart rate at triage	2.44	1.98	3.02
Highest heart rate	2.74	2.24	3.35
Diastolic blood pressure at triage	2.66	2.19	3.23
Diastolic blood pressure at disposition	2.66	2.19	3.23
Systolic blood pressure at triage	2.06	1.64	2.59
Systolic blood pressure at disposition	2.62	2.03	3.42
Blood thinners	3.62	2.84	4.45
International normalized ratio	6.02	4.65	7.91
Hemoglobin	10.77	8.45	13.68
Hematocrit	12.26	9.88	15.21
Dementia	2.68	2.08	3.44
Nursing home resident	3.09	2.40	3.99
Creatinine	2.49	2.02	3.07
Blood Urea Nitrogen	5.04	3.92	6.48

Odds ratio between predictors that showed to have collinearity and the outcome

4.9 Multivariable regression analysis

4.9.1 Predictor variables

We considered the following 18 variables for multivariable regression analysis:

- Demographics: **age, from nursing home**
- Presenting symptoms: **melena**
- Physical examination: **positive digital rectal examination, bloody stool in the ED**
- Vital signs at triage: **heart rate, DBP, SBP**
- Past medical history: **diverticulosis**, **colorectal polyps, previous gastrointestinal bleeding, tumor**
- Medication use**: aspirin, NSAIDs, protonpump inhibitors**
- Laboratory values: **hemoglobin, INR, blood urea nitrogen**

4.9.2 SELECTION=SCORE option and backwards selection

SELECTION=SCORE

We used the SELECTION=SCORE function in SAS on all 10 datasets from the multiple imputation database, aiming for a model with 5 predictors. Table 17 gives an overview of the selected predictors per dataset. We found that the following 5 predictors were statistically significant in 10/10 of the datasets.

- Age ≥75 years
- INR ≥2.0
- Hemoglobin ≤100 g/L
- Clear red bloody stool in the ED
- Past medical history of colorectal polyps

No other predictors were found to be significant with this method.

The Hosmer-Lemeshow test was >0.05 and ranged between 0.10-0.23 in all datasets. The area under the ROC curve varied from 0.85-0.86 in all 10 datasets.

Table 17	Selection=Score	Datasets									
		1	2	3	4	5	6	7	8	9	10
Demographics	Age ≥75 years										
	Nursing home										
Symptoms	Melena										
	Positive digital rectal examination										
	Bloody stool in ED										
Vitals at triage	Heart rate ≥100 bpm										
	Diastolic blood pressure ≤70 mmHg										
	Systolic blood pressure ≤110 mmHg										
Past medical history	Diverticulosis										
	Colorectal polyps										
	Previous gastrointestinal bleed										
	Tumor										
Medications	Aspirin										
	Nonsteroidal anti inflammatory drugs										
	Protonpump inhibitors										
Laboratory values	Hemoglobin ≤100 g/L										
	International Normalized Ratio ≥2.0										
	Blood Urea Nitrogen ≥15										
	Hosmer Lemeshow	0.096	0.134	0.228	0.104	0.111	0.099	0.101	0.134	0.127	0.096
	Receiver Operator Curve	0.847	0.856	0.851	0.848	0.846	0.846	0.848	0.856	0.847	0.846

Applied the SELECTION=SCORE option on the 10 datasets derived after multiple imputation. The 10 datasets are displayed in the vertical columns. A green box means that the predictor is selected in that specific dataset as significant in a multivariate regression model. The Hosmer Lemeshow and Area Under Receiver Operator Curve are reported for each dataset.

Backwards selection

In table 18 a summary of the results of backwards selection per dataset of the multiple imputation database is provided.

An INR ≥2.0, a past medical history of colorectal polyps datasets and a hemoglobin of ≤100 g/L were statistically significant in 10/10 datasets; age over 75 years was included in 9/10 datasets, a bloody stool in the ED in 8/10 datasets and a positive DRE in 1/10 datasets. .

The Hosmer-Lemeshow was >0.05 and varied from 0.10-0.17. The area under the ROC curve varied from 0.79-0.86. There was 1 dataset with an area under the ROC curve below 0.8, dataset 3, which consisted of a hemoglobin ≤100 g/L, INR ≥2.0, a bloody stool in the ED and a medical history of colorectal polyps.

Table 19 provides for a comparison of the predictor selection with both the selection=score option and the backwards selection method. An INR ≥2.0, age ≥75 years and a history of colorectal polyps was chosen in 10/10 databases with both the selection=score option and with the backwards selection method. A hemoglobin of ≤100 g/L was chosen in 10/10 datasets with the selection=score option, and in 9/10 datasets with the backwards selection method. A clear bloody stool in the ED was also chosen in 10/10 datasets with the selection=score option and in 8/10 datasets with the backwards selection option. A positive DRE was significant in 1/10 datasets with the backwards selection method, and was not significant in any dataset with the selection=score option.

Table 18	Backwards selection	Datasets									
		1	2	3	4	5	6	7	8	9	10
Demographics	Age ≥75 years										
	Nursing home										
Symptoms	Melena										
	Positive digital rectal examination										
	Bloody stool in ED										
Vitals at triage	Heart rate ≥100 bpm										
	Diastolic blood pressure ≤70 mmHg										
	Systolic blood pressure ≤110 mmHg										
Past medical history	Diverticulosis										
	Colorectal polyps										
	Previous gastrointestinal bleed										
	Tumor										
Medications	Aspirin										
	Nonsteroidal anti inflammatory drugs										
	Protonpump inhibitors										
Laboratory values	Hemoglobin ≤100 g/L										
	International Normalized Ratio ≥2.0										
	Blood Urea Nitrogen ≥15										
	Hosmer Lemeshow	0.096	0.134	0.103	0.104	0.165	0.099	0.101	0.134	0.127	0.130
	Receiver Operator Curve	0.847	0.856	0.785	0.848	0.820	0.846	0.848	0.856	0.847	0.843

Applied backward selection logistic regression with a p <0.01 to the 10 datasets. Every column represents 1 dataset from the multiple imputation database. A green boxes is a significant variable in that specific dataset. The Hosmer Lemeshow and Area Under Receiver Operator Curve are displayed for every dataset.

Table 19		
	SELECTION=SCORE option (n/10 datasets)	**Backwards selection (alpha <0.01) (n/10 datasets)**
INR ≥2.0	10	10
History of colorectal polyps	10	10
Hemoglobin ≤100 g/L	10	10
Age ≥75 years	10	9
Clear bloody stool	10	8
Positive DRE	0	1

Predictors selected with the selection=score option and backwards selection regression analysis.

4.9.3 Final model

The following 5 predictors showed to be the most significant predictors in a logistic regression model:

- Age ≥75 years
- INR ≥2.0
- Hemoglobin ≤100 g/L
- Clear red bloody stool in the ED
- Past medical history of colorectal polyps

We combined the estimates of the logistic regression model of the 10 datasets, using the Rubin's rules (62). In table 20 an overview of the final estimates with 95% CIs using Rubin's rule is provided.

Table 20					
	Estimate	**Standard error**	**95% CI**		**P-Value**
			Upper	Lower	
Intercept	-3.548	0.362	-4.257	-2.83876	<0.0001
Age ≥75 years	0.995	0.375	0.261	2.461	0.008
International Normalized Ratio ≥2	1.530	0.475	0.599	2.54	0.001
Hemoglobin ≤100 g/L	2.061	0.434	1.210	2.912	<0.0001
Bloody stool in ED	1.237	0.434	0.387	2.086	0.004
PMHx of colorectal polyps	1.321	0.401	0.535	2.106	<0.0001

Combining estimates of the 10 datasets derived from the multiple imputation database with the Rubin's Rule

We found that the following model represented the optimal model:

Log[odds (ever experienced one of the components of the composite adverse outcome)] =
-3.548 + 0.995 (if **age ≥75 years**) + 1.530 (if **INR ≥2.0**) + 2.061 (if **hemoglobin ≤100 g/L**) + 1.237 (if **bloody stool in the ED**) + 1.321 (if **history of colorectal polyps**).
When applying this model to our original database the model had a AUC of 0.83 (95% CI 0.77-0.89). The Hosmer Goodness-of-Fit test was 0.2702.

To retrieve the final model, we rounded estimates that ended with < .5 down and estimates that ended to be ≥ .5,up. Thus, a patient could get 1 point for age ≥75 year, a bloody stool in the ED and a history of colorectal polyps. Patients would get 2 points for a hemoglobin ≤100 g/L or an INR ≥2.0. The maximum score a patient could get with this score is 7.

4.10 Recursive partitioning

We used the same 18 predictor variables as we used at the start of our multivariable analysis. Through recursive partitioning, our data only split 1 time, which was for age more than 75 years. Please see figure 2 for an overview of the recursive partitioning.

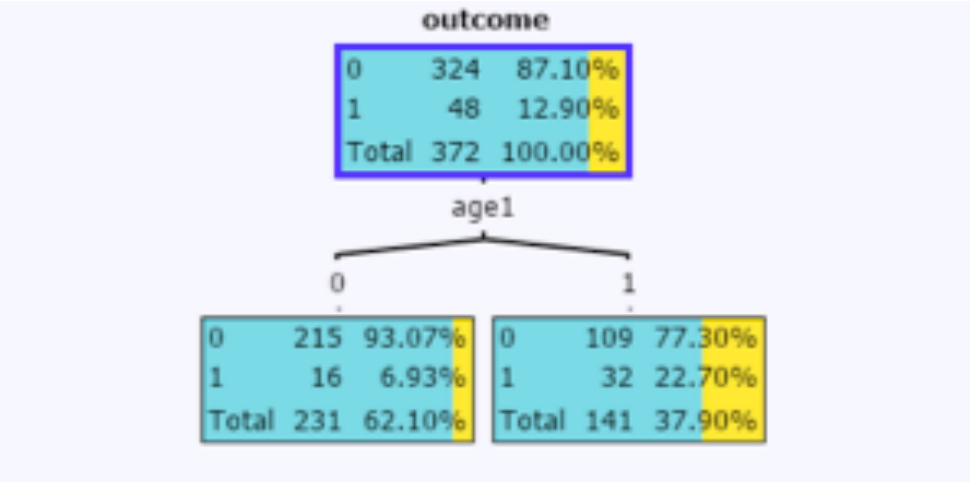


Figure 2: One split was created with recursive partitioning in KnowledgeSeeker

4.11 Diagnostic accuracy

We calculated the sensitivity, specificity, negative and positive predictive value for the logistic regression model that we developed in this study. We calculated these diagnostic parameters for different cut-off scores from 1 to 7.

We divided the database in the following groups in order to calculate the diagnostic accuracies for different cut-off scores:

1. Being positive for 0 predictors vs. being positive for 1 or more predictors
2. Being positive for 0 or 1 predictor vs. being positive for 2 or more predictors
3. Being positive for 0, 1 or 2 predictors vs. being positive for 3 or more predictors
4. Being positive for 0, 1, 2 or 3 predictors vs. being positive for 4 or more predictors
5. Being positive for 0, 1, 2, 3 or 4 predictors vs. being positive for 5 or 6 predictors.
6. Being positive for 0, 1, 2, 3, 4 or 5 predictors vs. being positive for 6 or 7 predictors.
7. Being positive for 0, 1, 2, 3, 4, 5 or 6 predictors vs. being positive for 7 predictors.

In table 21, an overview of these diagnostic accuracies for all the cut-off scores is provided. When using a cut-off score of 1, the sensitivity was 0.96 (95% CI 0.90-1.00), however the specificity was 0.53 (95% CI 0.48-0.59). The sensitivity was 0.69 (95% CI 0.55-0.82) and the specificity was 0.76 (95% CI 0.70-0.81) when a cut-off score of 2 was used. When using higher cut-off scores, the sensitivity became lower and the specificity became higher.

The positive LR was 2.06 for a cut-off score of 1, and increased to 16 for a cut-off score of 6. The negative LR was 0.08 for a cut-off score of 1 and increased to 0.9 for a cut-of score of 6.

Table 21						
Cut-off scores	**Sensitivity**	**Specificity**	**PPV[a]**	**NPV[b]**	**Positive LR[c]**	**Negative LR[c]**
0 vs. ≥1	0.96 0.90-1.00	0.53 0.48-0.59	0.23 0.17-0.29	0.99 0.97-1.00	2.06 1.80-2.34	0.08 0.02-0.30
0-1 vs. 2-7	0.69 0.55-0.82	0.76 0.70-0.81	0.34 0.25-0.44	0.93 0.89-0.97	2.84 2.11-3.82	0.41 0.26-0.64
0-2 vs. 3-7	0.49 0.35-0.63	0.91 0.86-0.94	0.49 0.35-0.63	0.91 0.86-0.94	4.93 3.06-7.97	0.57 0.43-0.75
0-3 vs. 4-7	0.33 0.20-0.47	0.98 0.97-1.00	0.73 0.54-0.91	0.91 0.88-0.94	18.00 7.41-44.00	0.68 0.56-0.83
0-4 vs. 5-7	0.11 0.00-0.23	0.99 0.98-1.00	0.60 0.17-1.00	0.93 0.89-0.95	16.00 2.80-92.00	0.90 0.78-1.02
0-5 vs. 6-7	0.03 0.00-0.06	1.00 1.00-1.00	1.00 1.00-1.00	0.87 0.84-0.91	Inf 0.82-482.00	0.98 0.92-1.02
0-6 vs. 7*						

Diagnostic accuracies per cut-off score with 95% confidence intervals.

[a] PPV = Positive predictive value

[b] NPV = negative predictive value

[c] LR = Likelihood Ratio

* * No patients had a score of 7

5. Discussion

5.1 Summary of results

This health records review is an exploratory analysis to aid future research in developing an accurate clinical decision tool to risk-stratify ED LGIB patients.

We found five suitable predictors using logistic regression: **age ≥75 years, INR ≥2.0, hemoglobin of ≤100 g/L, clear red bloody stool in the emergency department** and **a past medical history of colorectal polyps**. We chose the combination of these five variables based on clinical relevance, statistical significance, reliability, goodness of fit and predictive value. The ROC was 0.83 (95% CI 0.77-0.89), sensitivity 0.96 (0.90-1.00) and specificity 0.53 (0.48-0.59) for a cut-off score of 1.

5.2 Explanation of predictors

It is no surprise that age ≥75 year was selected for the final model. Older people are more likely to have an adverse outcome after an LGIB, as they are generally more frail and have more comorbidities compared to a younger population. There is more often polypharmacy that can negatively affect their outcome. Further, older people are at higher risk of cognitive issues, which can affect self-care. Also, they have less access to health care as they depend more often on a third party (family, paramedics) to get to the hospital (64, 65).

A hemoglobin of ≤100 g/L can be a sign of significant blood loss. Hemoglobin is a protein in red blood cells, and the level drops during bleedings. However, immediately after an acute bleed the hemoglobin level stays at baseline as the patient is losing whole blood. After several hours, the blood vessels will fill with extravascular fluids, which will dilute the blood and cause a drop in the hemoglobin level. Therefore, it is a good indicator for blood loss in patients who present to the ED with a rectal bleed.

Patients who have a clear red bloody stool in the ED have an ongoing bleeding. Most bleeds resolve spontaneously, so patients who have an ongoing bleeding in the ED might need an intervention in order to stop the bleeding. Therefore, it seems reasonable that this predictor made the final model.

Patients with a past medical history of colorectal polyps could present to the ED with LGIB because these polyps are causing their bleed. If that is indeed the reason for their rectal bleed, they are more

prone to rebleeds from these sites without an intervention. However, it is unclear why this would be a better predictor than other features from a GI related past medical history, like diverticulosis or colon cancer.

INR reflects the time it takes to form a blood clot. A normal INR is 1.0, but it can be prolonged by medications like vitamin K antagonists or by liver failure. Our final model included an INR of ≥2.0, which indicates a prolonged bleeding time which could result in needing intervention to stop the bleeding and easy rebleeding from sites that are prone to bleeding. In our study, more than 25% of patients did not have an INR measured during their emergency visit. As we reasoned that INR has a high clinical importance, we decided to keep it in the model and to impute an INR to patients with missing data based on other demographic information. Despite this, we think it is fair that INR was chosen in the multivariable regression analysis as it is a clinical important predictor and the assumption under which we imputed the data was clinically substantiated.

5.3 Reasoning behind predictor selection

As explained in the methods, we first excluded variables based on missing data, a low cell count, univariate analysis and reliability. We then considered collinearity between the remaining predictors in order to find the final 18 potential predictors that were considered for multivariable regression analysis. Please see below the rational for the decisions that were made for predictor selection.

5.3.1 Missing data

We excluded predictors that had >25% missing data as we couldn't guarantee accuracy when including these variables.

It is important to identify the type of missing data in a database, as it will determine the statistical approach one can use to handle the missing data. Handling missing data appropriately will lead to decreased risk of bias and improved validity of the results.

There are three types of missing data identified in epidemiology: data missing completely at random (MCAR), missing at random (MAR) and missing not at random (MNAR). Missing completely at random occurs when the missing data does not depend on other missing or observed data, and this data can be dealt with using multiple imputations. If the missing data are at random, it means that the probability of missingness depends on observed data but not on the missing data. Data that is MAR

can also be imputed with multiple imputations. Data are MNAR if the missing data depends on the unobserved, missing data itself. Missingness completely at random can be statistically tested for, but it is hard to statistically differentiate between MAR and MNAR.

There are several ways to handle missing data.

- Listwise deletion: This can be done with data missing completely at random, and results in deletion of all cases with one or more missing value are deleted from the database. This would reduce our total sample size significantly, which would not be feasible for this thesis project.
- Single imputation method: This refers to imputing the missing value with a plausible value, for example the mean of all the non-missing values. The advantage is that the sample size remains the same, however the distribution of the data can be distorted with this technique.
- Multiple Imputation: Multiple datasets within one database are created with different imputed values. This technique can only be used when the data are not MNAR (66, 67).

We found higher proportions of missing data among the patients who did not receive an outcome compared to people who did compare an outcome (table 11). We could only speculate that less sick patients have less details regarding the predictor variables documented which leads to more missing data. However, having the predictor variables recorded might be a prognostic factor in itself for a worse outcome. As this is a retrospective study, it is possible that we missed information that was not documented on the charts. We therefore potentially missed certain medical illnesses in our analyses, which could lead to misclassification bias. As it is hard to track down if and how the misclassification is related to the outcome, it is unsure if this caused differential or nondifferential misclassification. Differential misclassification occurs when the errors in past medical history are related to the outcome. If this would have happened, we would potentially have missed certain predictors which hypothetically would change our regression model. Nondifferential misclassification occurs if the misclassification of the past medical disease is not related to the outcome and this would have no effect on the regression model.

We concluded that the missing data are associated with the outcome, and therefore thought that the data was not MCAR but we could not differentiate if the data was MAR or MNAR. Acknowledging this, we chose for multiple imputations to handle the missing data.

5.3.2 Collinearity

Collinearity occurs when two or more variables are associated with each other. Including variables that show to have (multi)collinearity in a model can inflate the variances of the parameter estimates, wrong signs and magnitude of logistic regression coefficient estimates which can lead to incorrect conclusions. Confidence intervals are generally wide. It will also make it difficult to get good estimates of the effect of each individual parameter.

There are several ways to deal with (multi)collinearity. One way can be to combine two variables in one single variable. For example, in our data there was collinearity between "dementia" and "nursing home resident". It would have been possible to make one new variable out of these two variables: "having dementia or living in a nursing home". Another way of dealing with collinearity is by removing one of the variables, however there is no statistical test to tell which variable should be removed. Further, you could potentially remove an important variable that will not be considered for the final model. One way to handle this is to replace the removed variable with another important variable with no multicollinearity. Acknowledging the limitations, we decided to remove one of the predictor variables that showed to have collinearity based on clinical relevance and statistical significance (odds ratios, table 16).

There was collinearity between DBP at triage and at disposition. Both variables had the same OR for experiencing the outcome (2.66, 95% CI 2.19-3.23). However, we reasoned that DBP at triage is a more reliable predictor compared to this measurement at disposition as the disposition time differs for all the patients and is affected by treatment given and response to treatment. Therefore, we considered DBP at triage in the multivariable regression analysis. For the same reason we considered SBP and heart rate at triage over SBP at disposition and the highest heart rate in our final analysis.

Hemoglobin and hematocrit showed to have collinearity and were equally associated with the outcome. As we reasoned that hemoglobin would be more widely used by clinicians, we included this variable in our multivariable regression analysis.

Both creatinine and blood urea nitrogen (BUN) are surrogate biomarkers for renal function, and these variables can be increased with a decreased renal function and with dehydration (e.g. due to blood loss). The OR for BUN with the outcome was almost twice as high compared to creatinine. Therefore, we included BUN in the multivariable regression analysis.

Age and cardiovascular disease showed to have collinearity and were associated with the outcome with the same strength. We reasoned that age is a more reliable variable in a retrospective study than having a cardiovascular comorbidity. Therefore, we chose age ≥75 years for the final analysis.

Taking blood thinning medication and an INR ≥2.0 showed to have collinearity. INR was more strongly associated with the outcome than blood thinning medications. In a retrospective study an INR value is more reliable than "taking blood thinning medication" documented on a chart. However, in our study 48% of INR was missing which decreases the reliability of this predictor variable. We imputed the 48% missing data for INR based on the mean INR in people who did and who did not use anticoagulants, the predictor variable that influences INR the most. Therefore, we partly combined the two variables that showed collinearity.

Eventually, we used 18 variables in the multivariable regression analysis. There were 2 demographic related variables (age and living in a nursing home), 1 presenting symptom (melena along with BRBPR), 2 physical examination variables (positive DRE and bloody stool in the ED), 3 vital signs at triage (HR, SBP DBP), 4 variables related to the past medical history (diverticulosis, colorectal polyps, previous GI bleed, tumor), 3 medication-related predictors (aspirin, NSAIDs, proton pump inhibitor), and 3 laboratory values (hemoglobin, INR, BUN).

We aimed to keep the final model to a minimum given the number of study outcomes in order to prevent overfitting. We used the SELECT=BEST option on the 18 variables on every dataset of the multiple imputation database, in order to get the best 5 variables based on AIC. We also used backwards selection with a p-value of <0.01 and found the same 5 predictor variables to be significant in most datasets with this method. With recursive partitioning we only found 1 predictor that seemed to predict the outcome: age over 75 years. The Hosmer-Lemeshow showed goodness-of-fit in 10/10 databases and the ROC ranged from 0.85 to 0.86 when applying the 5 predictors to all 10 datasets, which indicates that the model has a good predictive value.

5.3.3 Interaction

We did not incorporate interaction between variables in our final model, as this would increase the chance for overfitting. Clinically, we assumed there would not be a significant interaction. However, we did not statistically test this as we determined we did not want to incorporate it in the final model.

5.3.4 Comparing models

We intended to compare logistic regression analysis and recursive partitioning. There was only 1 split with recursive partitioning (age ≥75 years) and we decided to not further analyse this, as a prediction with 1 generic variable will not aid ED physicians in their management.

5.4 Optimal cut-off score

In general, an optimal clinical decision tool should have a high sensitivity and high specificity. We calculated the sensitivity, specificity, PPV, NPV, positive and negative likelihood ratios for the 7 different cut-off scores and found that none of the cut-off scores had both a high sensitivity and high specificity.

A score with a high sensitivity is able to accurately identify low-risk patients. In this scenario, patients with a low score have a low risk of experiencing the outcome. So if we develop a risk score with a high sensitivity and a patient has a low score, we are able to say that it is likely that this patient is safe to treat as an outpatient. On the contrary, a high specificity is able to identify patients at high risk of experiencing an outcome. Thus, if a patient is identified as a high-risk patient by having a high score, it is likely that this patient will experience an outcome. If we would develop a risk tool with just a high specificity but a low sensitivity, it would be difficult to identify the low risk patients, which would lead to overtreatment and higher health care cost. That is why it was our priority to find a high sensitivity over a high specificity. This would enable the physician to identify the low-risk patient and safely discharge them home, while the intermediate and high-risk patients would be treated as an inpatient. When using a cut-off score of 0 vs. ≥1, we found the highest sensitivity of 0.96. Therefore, we think that this cut-off score is the optimal score for use in clinical practice based on this study.

However, again, an ideal risk score would have both a high sensitivity and specificity.

5.5 Comparison with previous studies

In this paragraph, we will compare the existing scores with the model that we developed with our analysis. Please see table 22 for a summary of this discussion.

5.5.1 BLEED score

The BLEED score was developed in 1995 in order to triage patients with a gastrointestinal bleed who would benefit from admission to the ICU (25). The score was validated in 1997: all patients who met 1 of the BLEED criteria were “high-risk patients”; patients who did not meet any of the criteria were classified as low-risk. This distribution in cut-off score is similar compared to the cut-off scores in our

study: patients have either 1 or more characteristics of the score and are at increased risk of developing an outcome, or they have 0 characteristics and don't have an increased risk of experiencing the outcome.

The similarity in predictors in the BLEED score and our model is that both models incorporate having an ongoing bleeding in the ED and an prolonged bleeding time. The BLEED score uses an prothrombin time >1.2 times compared to the control group, while we used an elevated INR of ≥2 which both indicates a prolonged bleeding time.

The other predictors that are included in the BLEED score differ from the predictors chosen in our analysis. The BLEED score uses a SBP lower than 100 mmHg, while this was not significantly associated with the outcome in our multivariable analysis. It was part of the 18 variables selected after the univariate analysis, but was not significant in a multivariable regression model.

The BLEED score used "erratic mental status" which was defined as any notation in the ED chart suggesting "clouding of consciousness due to any cause". This seems like an unreliable and vague description, which is difficult to replicate. Also, this variable is difficult to collect in a retrospective manner. We did collect data on the GCS, which can be a surrogate for mental status, but excluded this variable as the missing data rate was >25%.

The BLEED score also includes "unstable comorbid disease", defined as "any organ system abnormality that ordinarily would require ICU admission". This, again, is a very broad and vague term and could be interpreted differently by different health care providers and therefore makes this a variable that is difficult to replicate.

The advantage of the BLEED score over our score is that the BLEED score was derived prospectively. However, the BLEED score was focused on triaging ED patients to the ICU and excluded all discharged patients. Our study is more focused on the ED physician and patient population, as we included ED patients who were admitted and discharged. Further, the BLEED score was developed for lower and upper GI bleed, and there were only 13 patients with a lower GI bleed included in the derivation study. Therefore, our study is also superior over the BLEED score in terms of sample size. The AUC of the BLEED score was 0.72 (study did not provide confidence intervals), while our AUC for the ROC curve was 0.85. Our study provides stronger evidence regarding risk-stratification in ED LGIB patients than the BLEED score.

5.5.2 Strate et al.

Strate et al. developed a risk score to identify patients who were at risk of a severe lower intestinal tract bleeding (6, 27). Severe LGIB was defined as continued bleeding within the first 24 hours (requirement of at least 2 units PRBCs and/or a decrease in hematocrit of ≥20%) and/or a recurrent bleeding after 24 hours of clinical stability. About 48% of the patients met these criteria. The higher occurrence rate of adverse outcomes in this study compared to our study can be explained by the different patient population and study setting (hospital in the US, patients were included from 1996 until 1999) and by the definition of "severe LGIB", which differed from the outcome we used in this study. Both Strate et al. and our final model included ongoing bleeding in the ED as a predictor. Further, Strate et al. also included heart rate ≥100/min, SBP, syncope, a non-tender abdominal examination and >2 active comorbid conditions in their model, which were not included in our final model. Syncope and abdominal pain on palpation were excluded from our analysis, as it showed no relation with the outcome during the univariate analysis. A heart rate ≥100/min and SBP were excluded in the multivariable analysis.

Age and INR were not identified as statistical significant in the study by Strate et al. For age, this might be due to the different cut-off score they used (66 vs. 75). The study of Strate et al did not evaluate the significance of hemoglobin in their analysis, while this was our strongest predictor.

Both our study and Strate et al. were retrospective studies. Strate et al. only included admitted patients while, again, we included patients who were admitted into hospital or discharged home which is more useful in the context of an emergency department. Our outcomes were more relevant to ED physicians compared to Strate et al: mortality, recurrent bleeding and need for intervention within 30 days after ED discharge vs. continued bleeding or readmission to the hospital within 1 week of discharge. The area under the ROC curve derived in our study was higher compared to Strate et al (0.85 vs. 0.76, Strate et al. did not report confidence intervals).

5.5.3 Velayos et al.

In this prospective study from Velayos et al. with 94 patients, 37 patients (39%) had severe LGIB, which was defined as ongoing bleeding or rebleeding after leaving the ED (7). This was further specified as gross rectal bleeding along with abnormal vital signs or a transfusion of >2 PRBCs during hospitalization.

This study found the following 3 independent variables for predicting severe LGIB: hematocrit ≤35%; abnormal vital signs after 1 hour (SBP <100 mmHG or HR >100/min); and gross blood on initial rectal

examination. Only hematocrit was significantly associated with the outcome when using multivariable regression.

There are some similarities in predictors when comparing our study with Velayos et al; their score included hematocrit, which this was also very strongly associated in our univariate analysis. However, we did not include this in our multivariable regression analysis, as it showed to have collinearity with hemoglobin. Hemoglobin was highly significant and eventually chosen over hematocrit in our final analysis. Velayos included 2 vital signs: SBP and heart rate. They did not make the final cut in our regression model. Velayos et al. included gross blood on initial rectal examination, which was not included in our study. A similar predictor that we included is continued bleeding in the ED. Both predictors are indicators of bleeding that does not resolve spontaneously.

Velayos et al. did not find a significant association between age and the outcome, but they used a different cut-off compared to us (65 vs. 75). The reason that they might have chosen for a cut-off of 65 is due to their relative small sample size of 94. By increasing the cut-off for age, one of the two groups might have been too small for further analysis. This is only a speculation. This study did not analyse a past medical history of colorectal polyps.

Our study is superior over Velayos et al., as we had a larger sample size compared to their study. Further, Velayos et al. only included ED patients who were admitted with LGIB rather than both discharged and admitted patients. They analyzed the association between individual predictors and the outcomes, rather than creating a model. They did not report measures of diagnostic accuracies.

5.5.4 Artificial Neural Network model

The artificial neural network (ANN) used 20 variables for their decision tool to predict mortality, need for intervention and recurrent bleeding. The variables they included were **age**; **comorbidities** (cardiovascular disease, COPD, chronic renal failure, diabetes mellitus, dementia); **history** (diverticulosis, colonic arteriovascular malformations, NSAIDS, anticoagulants, residence in a nursing home); **features at presentation** (haematochezia, orthostatic symptoms); **features at initial assessment** (SBP <100 mm Hg, orthostatic signs); and **laboratory findings** (WBC, packed-cell volume, platelet count, creatinine, prothrombin time). An artificial network is a totally different approach, which makes their study hard to compare with ours. Continuous variables were not categorized but entered as continuous variables, which is probably better and prevents binning.

The ANN did include age, hematochezia and INR, however the ANN did not include hemoglobin or a past medical history of colorectal polyps in their analysis.

Statistically it is difficult to compare the artificial neural network with our study, as both studies used different statistical methods. The AUC for the ANN to predict the need for intervention was 0.95; 0.93 to predict recurrent bleeding; and 0.92 for in-hospital death. This is higher than the area under the ROC curve calculated for our risk score. The ANN did not report confidence intervals.
Our study is more feasible to use as we only included 5 variables compared to 20 variables. Using a decision tool with that many variables is a timely process in a busy emergency department and physicians might favour a tool that is easier to use, like our score. Further, this score also excluded patients who were discharged from the ED.

5.5.5 Gradient boosting algorithm

A gradient boosting algorithm was developed to predict therapeutic intervention, severe bleeding and recurrent bleeding after an initial LGIB bleed. This study included 170 patients in the internal validation cohort and 130 patients in the external validation cohort. Almost all (98-100%) patients were admitted for management of their LGIB. This alone tells us that the patient population is different than in our study where 28.2% of patients were admitted, which is presumably more in line with most Canadian health care centers.
The gradient boosting algorithm is also a different type of approach to select predictors for a clinical decision tool compared to the methods used in this study. The gradient boosting algorithm used 39 variables reflecting demographics, history, comorbidities, initial assessment and laboratory findings. This study used all of the variables that were also selected in our study. They found that INR, hemoglobin and a past medical history of colorectal polyps were among the top 10 of variables that were most contributing to the gradient boosting models. The accuracy of this model for predicting recurrent bleeding, therapeutic intervention and severe bleeding varied from 78-91% depending on which outcome was studied. Overall, the sensitivity was low (57%-80%) and the specificity was higher (80%-92%). As it is likely more important for ED physicians to identify patients at low risk in order to assure safe discharge, a high sensitivity would be more beneficial than a high specificity.
This model is not feasible to use by ED physicians due to the large amount of predictors that are included. This study also only included patients who were admitted to the hospital. This study did not report the area under the ROC curve, but the predictive accuracies for recurrent bleeding was 88%, for

need for intervention 91% and for severe bleeding 83%. This study also did not report 95% confidence intervals, which makes it difficult to compare with our study.

5.5.6 HAKA score

In this study, 83 of the 668 patients (20%) experienced severe LGIB. The four risk factors that were independently associated with the outcome were aspirin use, collapse, hemoglobin <100 and albumin <38. In our study, albumin was not used in the univariate analysis as it has >25% missing data. Syncope (or collapse) was excluded in the univariate analysis as it showed not to be significantly associated with the outcome. Hemoglobin was the only variable that was significant in both final models.

Age with a cut-off of 60 was significant in the univariate analysis but not in their multivariable analysis. INR with a cut-off of 1.2 was not significant in the univariate analysis. A past medical history of colorectal polyps and ongoing bleeding in the ED was not considered for univariate analysis.

The highest sensitivity for the HAKA score was 88% for a cut-off score of 1. This sensitivity was lower than the sensitivity for the decision tool found in our study, while our specificity is higher compared to the HAKA score (cut-off of 1): 52.9% vs. 44%. So, our sensitivity and specificity for a cut-off score of 1 are slightly better than the HAKA score, however this study did not report 95% confidence intervals. The HAKA score only looked at severe bleeding and did not include mortality or need for intervention in their outcome. Even though their outcome consisted of continued bleeding within the first 24 hours or readmission to the hospital for LGIB within 1 week of discharge, they followed patients for 2 years, which is long and irrelevant for the emergency department.

5.5.7 Summary

In summary, our study has a larger sample size than most of the studies that the other scores were derived in, except for the HAKA score. Together with the HAKA score, we were the only score who included both admitted and discharged patients rather than just patients who were admitted to the hospital. We had a feasible score with only 5 predictors in our final model. Our outcome was comprehensive including mortality, need for intervention and recurrent bleeding. Lastly, our AUC was higher or comparably high compared to the other scores. However, it is difficult to statistically compare the predictive value of all the scores, as none of the other studies reported 95% confidence intervals.

Table 22	Our study	BLEED	Strate et al	Velayos	ANN	GBA	HAKA
Demographics	Age ≥75 years				Age	Age	
					Nursing home		
Past medical history	Colorectal polyps	Presence of an unstable comorbid disease	> 2 comorbid conditions		Cardiovascular disease	Alcohol abuse	
					COPD[d]	Colorectal polyp	
					Chronic renal failure	Diabetes mellitus	
					Diabetes mellitus	Total n of co-morbidities	
					Dementia		
					Diverticulosis		
					Arteriovascular malformations		
Symptoms	Clear red bloody stool in the ED	Ongoing bleeding	Rectal bleeding in the first 4h of evaluation		Ongoing bleed per rectum		Syncope or dizziness
		Erratic mental status	Syncope		Orthostatic symptoms		
Physical examination		SBP[b] <100 mm HG	HR[c] ≥100 bpm	HR ≥100 bpm	Orthostatic sign	HR	
			SBP[b] ≤115 mmHG	SBP <100 mmHG	SBP[b] <100 mmHg	SBP[b]	
			Non-tender abdominal examination	Gross blood on rectal examination		DBP[g]	
						Positive DRE[h]	
Laboratory values	Hemoglobin ≤100 g/l	Elevated PT (>1.2 times the control value)		Hematocrit <35%	WBC[e]	Platelet count	Albumin <38 g/dl
	INR[a] ≥2.0				Packed cell volume	APTT, PTT, PT	Hemoglobin <100 mg/dl
					Platelet count	Hematocrit, hemoglobin	
					Creatinine	Hemoglobin	
					INR[a]	Urea, creatinine	
Medication			Aspirin		NSAIDs[f]	NSAIDs[f]	Aspirin use
					Anticoagulants	Anticoagulants	

Comparison between predictors chosen in our model compared to other risk scores that have been developed previously.

[a] INR = international normalized ratio
[b] SBP = systolic blood pressure
[c] HR = heart rate
[d] COPD = chronic obstructive pulmonary disease
[e] WBC = white blood cell count
[f] NSAIDs = non steroid anti-inflammatory drugs
[g] DBP = diastolic blood pressure
[h] DRE = digital rectal examination

5.6 Strengths

One of the strengths of this study is that we had a relatively large sample size compared to previous studies. Some of the previous studies included 19 and 39 variables, which is not feasible to use in the emergency department.

The goal of this study was to conduct a pilot study that can aid in a larger prospective derivation study for clinical decision tool. We evaluated all clinical variables that are thus far identified to our knowledge in the literature as potentially important in risk-stratifying ED LGIB but also UGIB patients. Therefore, in terms of variables, our study was more complete compared to other studies.

For sake of the thesis we calculated diagnostic measurements and we found that the 5 selected variables had a high AUROC varying from 0.85 to 0.86 in the datasets of our multiple imputation database, which indicates a good predictive value. It also had a high sensitivity of 0.96. Especially the high sensitivity is important in order to identify LGIB patients who are at low risk of experiencing adverse outcomes. The results of this study give great guidance for future larger prospective studies to develop a solid clinical decision tool.

As this was a health records review, it was very important to accurately collect data from patient charts. We assured accurate data-collection by having 10% of the charts checked by two experienced data-collectors and calculating the inter-observer agreement using a kappa-value. We also had build-in ranges for the predictors that were entered in our database, which enabled us to detect abnormal values and correct them timely.

5.7 Limitations

The first limitation of this study is that data were collected retrospectively, which makes the study more prone to misclassification. Unfortunately we did not have the time and financial resources to conduct a prospective study. That is the reason why this study should be used as a pilot study rather than a derivation of a decision tool.

Another limitation is that we only had 48 outcomes, which limited the number of predictors we could include in the final regression model. Ideally, we want to include 1 predictor per 10 outcomes in order to prevent overfitting, which means we should have included 5 predictor variables at the start of the multivariable regression analysis. However, in the scope of this pilot study we decided to include more variables. A larger study will allow for more outcomes and thus more predictor variables to choose from.

Further, one can argue about the fact that we chose a composite outcome of recurrent bleeding, need for intervention and death. Often in composite outcomes some components weigh heavier than other components, and potentially the clinically less important component drives the composite outcome. In our case, death can be valued as more important for patients and physicians than the other 2 components and most people required an intervention to stop the bleed. Despite these reservations, we chose for a composite outcome as we wanted to identify all patients who would benefit from admission, further monitoring and inpatient treatment; and to identify patients who could safely be discharged. It is also more feasible for physicians to use in clinical practice, as it will identify all of these high-risk patients instead of risk stratifying per separate outcome. Further, most the previous studies that have been done on this topic also use this composite outcome or elements of this composite outcome.

Another limitation is the inclusion of INR in our final model while 48% of the data was missing. We thoughtfully imputed the missing data however, this might decrease the reliability of this variable. A future prospective study will hopefully be better able to document that or this variable could possibly be combined with the use of anticoagulants as a new variable "INR >2.0 or taking anticoagulants".

5.8 Future research

This study is an exploratory study to identify risk factors that might serve as predictors in a risk score to risk-stratify ED LGIB patients. For the sake of the thesis, we did create a logistic regression and calculated the sensitivity and specificity. However, the results should not be generalized and should not yet be used by clinicians.

The next step should be a prospective, large, derivation study. A prospective study will ensure more accurate data collection. Due to the retrospective nature of this study, physicians who filled out the patients' charts might have used different definitions for certain symptoms, physical examination and past medical history related features. When conducting a prospective study, the predictor variables are defined prior to collecting them and hence this would ensure a more accurate and homogenous data collection compared to a retrospective study.

Further, the derivation of the risk score should be done in a larger study sample. In this study, 48 patients (12.9%) experienced an adverse outcome after ED discharge. A larger study would have a larger number of outcomes, which would affect the amount of predictors that can be used in the

multivariable regression analysis. There were 18 variables statistically and significantly associated with the outcome after conducting a univariate analysis, and ideally you want to enter more than 5 predictors in a multivariable regression. Future prospective derivation studies should aim for a larger cohort with more outcomes resulting in a solid risk tool.
After derivation of a risk score, the score should be validated in an external population after which it should be implemented in order to see the effect of use of the score on mortality, morbidity and ED LGIB related health care costs.

5.9 Implications

It is key for ED physicians to accurately risk-stratify ED LGIB patients. It is important to be able to identify patients at high risk of experiencing adverse outcomes, but it is also useful to correctly identify low risk patients in order to safely discharge them home and follow them up as outpatients. Even though disposition decisions can be made with clinical knowledge and gestalt, a risk score would decrease variability in practice among ED physicians.

We successfully conducted a pilot study that aids in a larger derivation study to develop a clinical decision tool for ED LGIB patients. However, the limitations should be kept in mind when thinking of using the score. At this stage we would not recommend for ED physicians to make disposition decisions based on our study. We recommend other clinicians to treat this study as a pilot study, and to repeat a similar study in a prospective way with consideration of the limitations identified in our study. The next step would be a validation study to verify the results from the derivation study in a different patient population.
If a solid risk score has been developed, physicians can use this in addition to their standard practice to aid them in their disposition decision regarding ED LGIB patients. Physicians will be able to identify high-risk patients and transfer them to a hospital with appropriate management capabilities. For low-risk patients they can decide to follow them up as outpatients.

Once a well-established score has been developed and validated, the implications on impact on health care should be assessed.

6. Conclusion

In this retrospective health records pilot study we identified 5 predictors that could potentially be used in a clinical decision tool for risk-stratification of ED lower gastrointestinal bleed patient: Age ≥75 years, INR ≥2.0, hemoglobin ≤100 g/L, clear red bloody stool in the ED and a past medical history of colorectal polyps. This model showed good ability to discriminate patients with and without serious outcomes as evidenced by the high AUC for the ROC curve and sensitivity. Future, large prospective studies should be done to derive a clinical decision tool after which it should be validated and implemented.

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Appendix

Case Record Form
Clinical Decision Tool for Lower Gastrointestinal Bleeding

Subject number: ____
Date Index Visit (DD/MM/YY): ____/____/____ 30-day cut-off (DD/MM/YY): ____/____/____

Date of birth (MM/YY): ___/___ **Sex**: ○ Female ○ Male
Age at index visit: |__|__|__| years

	Yes	**No**	**NA**
Excluded If yes, reason of exclusion.	○	○	○
• Gastrointestinal bleeding not likely lower GI source (no bright red blood per rectum per history; no bright red blood on the glove after digital rectal examination; no clear red blood stool during the ED visit)	○	○	○
• LGIB is not the primary symptom	○	○	○
• Patient diagnosed with LGIB while admitted for another condition	○	○	○
• Patient receives palliative care	○	○	○
• LGIB is due to a significant trauma requiring admission	○	○	○
• Patient is a non-Ottawa resident	○	○	○
• Other: _____			

Presenting symptom at the emergency department/inclusion criteria	**Yes**	**No**	**NA**
Bright red blood per rectum (BRBPR)	○	○	○
If yes, BRBPR in last 24h	○	○	○
If yes, amount of days:	|___|___|___|___| days		
Bright red blood during digital rectal examination	○	○	○
Clear red bloody stool during the ED visit	○	○	○
Melena	○	○	○
Other: _____	○	○	○

Case Record Form
Clinical Decision Tool for Lower Gastrointestinal Bleeding

Subject number: ___
Date Index Visit (DD/MM/YY): ___/___/___ 30-day cut-off (DD/MM/YY): ___/___/___

Symptoms at Index Visit			
	Yes	**No**	**NA**
Abdominal pain	○	○	○
Syncope	○	○	○
Light-headedness/dizziness	○	○	○
Chest pain	○	○	○
Shortness of breath	○	○	○
Tender abdominal examination	○	○	○
Change in bowel movement If yes: • Diarrhea • Constipation	○ ○ ○	○ ○ ○	○ ○ ○
Medical History			
	Yes	**No**	**NA**
Diverticulosis	○	○	○
Arteriovascular malformations	○	○	○
Colorectal polyps	○	○	○
Hemorrhoids	○	○	○
Peptic ulcer disease	○	○	○
IBD If yes: • Crohn's disease • Colitis ulcerosa	○ ○ ○	○ ○ ○	○ ○ ○
Gastrointestinal bleeding	○	○	○
If yes, date of most recent (dd/mm/yyyy): ___/____/_____			
Coronary Artery Disease If yes: • Angina • Prior MI	○ ○ ○	○ ○ ○	○ ○ ○
Congestive heart failure	○	○	○
Hypertension	○	○	○
Atrial fibrillation	○	○	○
Atrial flutter	○	○	○
Cerebrovascular disease If yes: • CVA • TIA	○ ○ ○	○ ○ ○	○ ○ ○
COPD	○	○	○
Asthma	○	○	○
Previous creatinine Date (dd/mm/yyyy): ___/___/____ Value: |__|__|__|			
Currently on dialysis	○	○	○
Diabetes mellitus	○	○	○
Dementia	○	○	○

Medical History Continued			
	Yes	**No**	**NA**
Malignant tumor **If yes, colon cancer**	○ ○	○ ○	○ ○
Metastasis	○	○	○
Lymphoma	○	○	○
Liver Disease If yes: • Cirrhosis • Portal Hypertension	○ ○ ○	○ ○ ○	○ ○ ○
HIV or AIDS	○	○	○
Depression	○	○	○
Family history of GI cancer If yes: • Upper GI cancer • Lower GI cancer	○ ○ ○	○ ○ ○	○ ○ ○
Medication use			
Aspirin	○	○	○
NSAIDs	○	○	○
Anticoagulants If yes: • **Vitamin K antagonist** • New oral anticoagulants	○ ○ ○	○ ○ ○	○ ○ ○
Proton pump inhibitors If yes: • Omeprazol • Lansoprazole • Esomeprazole Other: _____	○ ○ ○ ○ ○	○ ○ ○ ○ ○	○ ○ ○ ○ ○
Lifestyle			
Nursing home resident	○	○	○
Alcoholism	○	○	○
Smoking If yes: • Current smoker • Ex-smoker	○ ○ ○	○ ○ ○	○ ○ ○

Case Record Form
Clinical Decision Tool for Lower Gastrointestinal Bleeding

Subject number: _____
Date Index Visit (DD/MM/YY): ___/___/___ 30-day cut-off (DD/MM/YY): ___/___/___

Physical examination

	SBP	DBP	Heart rate	Oxygen saturation	Glasgow Coma scale
At triage	|___|___|___|	|___|___|___|	|___|___|___|	|___|___|___|	|___|___|
At disposition	|___|___|___|	|___|___|___|	|___|___|___|		
Lowest	|___|___|___|	|___|___|___|	|___|___|___|		
Highest	|___|___|___|	|___|___|___|	|___|___|___|		

Laboratory values

Values of blood work	
Hemoglobin	|____|____|____|
Hematocrit	. |____|____|____|
Platelets	|____|____|____|
International Standardized ratio (INR)	|____|____| . |____|
Activated partial prothrombin time	|____|____|____|
White blood cell count	|____|____| . |____|
Creatinine	|____|____|____|
Blood Urea Nitrogen	|____|____| . |____|
Bilirubin	|____|____|____|
Albumin	|____|____|____|

Disposition decision

	Yes	No	NA
Referred	○	○	○
If yes:			
• Surgery	○	○	○
• Internal Medicine	○	○	○
• Other: _____	○	○	○
Admitted	○	○	○
If yes:			
○ Surgery	○	○	○
○ Internal Medicine	○	○	○
○ ICU	○	○	○
○ Other:_____	○	○	○

Most likely ED diagnosis:

○ Hemorrhoids ○ Polyps ○ ColonCa
○ Angiodysplasia ○ Post-endoscopy ○ IBD exacerbation
○ Diverticolosis/-itis ○ Radiation proctitis ○ Other: _____

Case Record Form
Clinical Decision Tool for Lower Gastrointestinal Bleeding

Subject number: ____
Date Index Visit (DD/MM/YY): ____/____/____ 30-day cut-off (DD/MM/YY): ____/____/____

30-day outcome ○Yes ○No ○ NA ○ .W

	Yes	No	NA
Death If yes: In the ED?	○ ○	○ ○	○ ○
Recurrent bleeding	○	○	○
Need for intervention If yes: In the ED?	○ ○	○ ○	○ ○
Blood transfusion	○	○	○
• If blood transfusion, amount of packed cells: ▪ In ED: |____|____| ▪ After ED discharge |____|____|			
• Endoscopic intervention to stop the bleeding If yes: In the ED?	○ ○	○ ○	○ ○
• Angiographic intervention to stop the bleeding If yes: In the ED?	○ ○	○ ○	○ ○
• Surgical intervention to stop the bleeding If yes: In the ED?	○ ○	○ ○	○ ○
• ICU admission due to LGIB related conditions If yes: • Vasopressors used • Respiratory failure	○ ○ ○	○ ○ ○	○ ○ ○
• Dialysis	○	○	○
• Other	○	○	○

Endoscopy report outpatient clinic (Star Endoscopy) should be checked ○Y ○N
Coroner's list should be checked: ○Y ○N
Montfort/Queensway Carleton should be checked ○Y ○N

Ottawa Health Science Network Research Ethics Board/ Conseil d'éthique de la recherche du Réseau de science de la santé d'Ottawa

December 11, 2015

Dr. Venkatesh Thiruganasambandamoorthy
Ottawa Hospital - Civic Campus
Department of Emergency Medicine
Clinical Epidemiology Unit
1053 Carling Avenue, Room F658
Ottawa, ON K1Y4E9

Dear Dr. Thiruganasambandamoorthy:

Re: Protocol # 20150648-01H **Derivation of a Clinical Decision Tool for Predicting Adverse Outcomes among Emergency Department Patients with Lower Gastrointestinal Bleeding**

Protocol approval valid until - December 10, 2016

Thank you for the email of December 11, 2015 from Dr. R. Ramaekers. I am pleased to inform you that this protocol underwentdelegated review by the Ottawa Health Science Network Research Ethics Board (OHSN-REB) and is approved. No changes, amendments or addenda may be made to the protocol without the OHSN-REB's review and approval.

PLEASE NOTE: THE APPROVAL OF THIS PROTOCOL IS CONDITIONAL UPON A FULLY-SIGNED STUDY CONTRACT/AGREEMENT BETWEEN THE OTTAWA HOSPITAL RESEARCH INSTITUTE, THE PRINCIPAL INVESTIGATOR AND THE SPONSOR (OR AS OTHERWISE REQUIRED). YOU CANNOT START THE STUDY, OR BEGIN TO RECRUIT RESEARCH PARTICIPANTS INTO THE STUDY UNTIL THE STUDY CONTRACT/AGREEMENT HAS BEEN SIGNED BY ALL PARTIES, AND HAS BEEN RECEIVED BY THE OTTAWA HOSPITAL RESEARCH INSTITUTE'S CONTRACTS OFFICE. FOR FURTHER DETAILS, PLEASE CONTACT RENÉE TODD AT CONTRACTS@OHRI.CA OR AT 613-798-5555 EXT. 19843.

Please Note: The approval of this study allows the principal investigator and study team to begin data collection from The Ottawa Hospital only. However, this approval is contingent upon receipt of the Coroner's Office Letter of Support.

Please submit an amendment report to the OHSN-REB requesting approval to begin collecting information from the external locations once the required approvals/support from each of the external institutions (Montfort, Queensway Carleton Hospital, Ottawa Endoscopy and Day Surgery Centre, Reimer Clinic, and Provis Rudd Endoscopy Ottawa) have been obtained. The external approvals/support letters must be submitted with the amendment.

We will also require confirmation that any contracts/agreements with the above indicated external parties have been fully executed.

...2

Approval is for the following:
- Electronic OHSN-REB Application
- Derivation of a Clinical Decision Tool for Predicting Adverse Outcomes Among Emergency Department Patients with Lower Gastrointestinal Bleeding Study Protocol (Version 4) dated November 2015
- Clinical Decision Tool for Lower Gastrointestinal Bleeding Case Record Form, version dated October 1, 2015

If the study is to continue beyond the expiry date noted above, a Renewal Form should be submitted to the REB approximately six weeks prior to the current expiry date. If the study has been completed by this date, a Termination Report should be submitted.

The Ottawa Health Science Network Research Ethics Board (OHSN-REB) was created by the merger of both the Ottawa Hospital Research Ethics Board (OHREB) and the Human Research Ethics Board (HREB) for meetings held at the University of Ottawa Heart Institute.

OHSN-REB complies with the membership requirements and operates in compliance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans; the International Conference on Harmonization - Good Clinical Practice: Consolidated Guideline; and the provisions of the Personal Health Information Protection Act 2004.

Yours sincerely,

The Ottawa Hospital | L'Hôpital d'Ottawa

UNIVERSITY OF OTTAWA HEART INSTITUTE
INSTITUT DE CARDIOLOGIE DE L'UNIVERSITÉ D'OTTAWA

uOttawa

Ottawa Hospital Research Institute
Institut de recherche de l'Hôpital d'Ottawa

***Ottawa Health Science Network Research Ethics Board/* Réseau des sciences de la santé d'Ottawa Conseil d'éthique de la recherche**

ANNUAL RENEWAL REPORT

1. **REPORT DATE:**	06-12-2016
2a. Protocol Number:	20150648-01H
2b. Protocol Title:	Derivation of a clinical decision tool for predicting adverse outcomes among emergency department patients with lower gastrointestinal bleeding
3. Principal Investigator at The Ottawa Hospital:	Dr. V. Thiruganasambandamoorthy
4a. Co-Investigators:	Dr. J Perry

4b. Have any co-investigators been added or removed since the last approval? ☐ Yes ☒ No
If new investigators have been added, include a letter or Amendment Report with the Additional Co-Investigator page http://www.ohri.ca/OHSN-REB/forms/additional_co.doc **with their original signature.**

5a. Most recent approval 'expiry date':	~~31-12-2016~~ 10-12-2016
5b. Number of research participants who have provided consent **AND** enrolled into the study locally, since initial approval **(if this is the first renewal for this study)** **OR** last renewal report date **(if this is the 2nd/subsequent renewal for this study)** :	Retrospective study, consent is not provided. 473 people enrolled
5c. Total number of research participants who have provided consent **AND** enrolled at this site since initial OHSN-REB approval (if this number exceeds the currently approved sample size, then refer to Section 7):	Retrospective study, consent is not provided. 473 people enrolled
5d. Number of local withdrawals since initial OHSN-REB approval **(if this is the first renewal for this study)** **OR** last renewal report date **(if this is the 2nd/subsequent renewal for this study)**:	n/a
5e. Total number of withdrawals at this site since initial OHSN-REB approval:	N/A
5f. Reason for withdrawals:	N/A
6. Projected date of study completion (this should reflect the information provided in the initial application and/or the information provided in Section 7) **Note:** If the projected date of study completion has been extended, please confirm that there are sufficient funds and/or resources in place to extend the study to the new date you provide.	December 31, 2017

ANSWER ALL OF THE FOLLOWING QUESTIONS:

7a. ☒ Yes ☐ No Has there been a departure from previously approved research. If yes, please specify:

- Completion date change/sample size increase or decrease? ☐ Yes ☒ No
- Inclusion/exclusion criteria? ☐ Yes ☒ No

- Source of subject (participant) population? ☐Yes ☒No
- Source of volunteer population (if applicable)? ☒Yes ☐No
- Other? Describe: ☐Yes ☒No

7b. ☒ Yes ☐ No An amendment form has been submitted to the OHSN-REB for review of any of the above changes?
If yes, date approved: 24-11-2016

7c. ☐ Yes ☒No Have any unexpected side effects, adverse events, or findings been noted since last approval? Has the OHSN-REB been informed of these?
☐ Yes ☒ No If yes, date submitted:

7d. ☐ Yes ☒No Has any information appeared in the literature, or evolved from this or other similar ongoing studies, since the date of last approval that might affect the OHSN-REB's or the research participant's perception of the risks and benefits of the study? (If yes, provide this information and your assessment of it in the section on progress of the study). Has the OHSN-REB been informed of these? ☐ Yes ☒No If yes, date submitted:

7e. ☐ Yes ☒No Has the consent form been modified since last approval? Has the OHSN-REB been informed of these changes? ☐ Yes ☒ No If yes, date approved:

7f. ☐ Yes ☒No WRITTEN INFORMED CONSENT has been obtained throughout the life of the study and if recruitment is still open will continue to be obtained from all research participants, or their next-of-kin/legal representative.

7g. ☐ Yes ☒No Have any new conflicts of interest arisen since initial approval (if this is your first renewal for this study) **OR** last renewal report date (if this is the 2nd/ subsequent renewal for this study)?

If yes, provide details:

NOTE:

Attach an **ORIGINAL COPY** of the most recently **APPROVED** consent forms, if no changes have been made. (If recruitment is closed, the OHSN-REB does not require a copy of the consent form)

If the Patient Information Sheets and/or Consent Forms are being revised, attach a copy of the revised documents with **ALL CHANGES HIGHLIGHTED**; and a clean, final version of the **REVISED** documents printed **ON ORIGINAL LETTERHEAD**.

Consent Forms and the study are approved for a maximum duration of one year only and must be validated by the board annually.

8. In the space below, briefly describe the progress of the study to date. Renewals cannot be considered **if this section is not complete.**

If zero participants have been enrolled since initial approval (if this is your first renewal for this study) **OR** last renewal report date (if this is the 2nd/ subsequent renewal for this study) please provide an explanation.

PLEASE TYPE OR PRINT CLEARLY

We have collected data of 473 patients who presented to the TOH ED with a lower GI bleed. We have analysed this data and written up the preliminary results. We recently got REB approval to go to the QCH, Coroner's office and Star Endoscopy Ottawa clinic to collect data of patients who were lost to follow up from the Ottawa Hospital. We will collect this data in the next few weeks.

We would like to get an extension of our study and REB approval, in order to finish the study. We can assume the study will be fully completed by 31-12-2017, and hope REB approval can be extended until then. We have enough resources and funds to continue and complete the study by this time.

Dec 08/2016

Date

PLEASE NOTE: ***You must keep a copy of this form for your study file.***

Ottawa Health Science Network Research Ethics Board/ Conseil d'éthique de la recherche du Réseau de science de la santé d'Ottawa

November 24, 2016

Dear Dr. Thiruganasambandamoorthy:

Re: Protocol # 20150648-01H Derivation of a Clinical Decision Tool for Predicting Adverse Outcomes among Emergency Department Patients with Lower Gastrointestinal Bleeding

Thank you for your Protocol Amendment Report dated Mar 23, 2016 which is approved.

The following are acknowledged:

-Letter of Support from the Ontario Office of the Chief Coroner dated January 5, 2015
-Letter of Support from the Montford Hospital dated March 4, 2016
-Letter of Support from the Star Endoscopy Clinic received in our offices March 24, 2016

-Copy of the Research Agreement with the Coroner's office dated January 21, 2016
-The aprroval Letter form the Montord Research Ethics Committee dated March 4, 2016
-The data Sharing Agreement with the Star Endoscopy Clinic received in our offices Mar 24, 2016

Ethical approval remains until December 10, 2016.

PLEASE NOTE: THE APPROVAL OF THIS PROTOCOL IS CONDITIONAL UPON A FULLY-SIGNED STUDY CONTRACT/ AGREEMENT BETWEEN THE OTTAWA HOSPITAL RESEARCH INSTIUTE, THE PRINCIPAL INVESTIGATOR AND THE SPONSOR (OR AS OTHERWISE REQUIRED). YOU CANNOT START THE STUDY OR BEGIN TO RECRUIT RESEARCH PARTICIPANTS INTO THE STUDY UNTIL THE STUDY CONTRACT /AGREEMENT HAS BEEN SIGNED BY ALL PARTIES, AND HAS BEEN RECEIVED BY THE OTTAWA HOSPITAL RESEARCH INSTITUTE'S CONTRACTS OFFICE. FOR FURTHER DETAILS, PLEASE CONTACT CONTRACTS ADMINISTRATION AT CONTRACTS@OHRI.CA OR AT 613-798-5555 EXT.19843.

...2

OHSN-REB complies with the membership requirements and operates in compliance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans; the International Conference on Harmonization - Good Clinical Practice: Consolidated Guideline; and the provisions of the Personal Health Information Protection Act 2004.

[Print]

Form ID: 4390
Status: Application - New
Created: 22-Jul-2015
Created By: rramaekers
Last Updated: 8/17/2015 2:25:06 PM

Protocol Title: Derivation of a Clinical Decision Tool for Predicting Adverse Outcomes among Emergency Department Patients with Lower Gastrointestinal Bleeding
Review Type: Delegated/Expedited Review
Principal Investigator: Venkatesh Thiruganasambandamoorthy

23. Division/Department/Program Approval (This should not be completed by the Principal Investigator, Responsible Site Investigator and/or Co-Investigators)

Hospital and university administrators share responsibility for research activities within their division, department or program. The purpose of this signature section is to ensure that administrators at research sites are aware of: a) the research activities undertaken in their division, department or program and b) the impact of these activities on the resources of their division, department or program and the patients and the communities they serve.

I have reviewed this application and by signing below, I certify that:

a) the study is consistent with hospital/faculty policies and mission

(•) Yes ( ) No ( ) Not applicable

b) the study resources (budget, space, and support staff) and/or the resources of my division, department or program are adequate to support the study,

(•) Yes ( ) No ( ) Not applicable

c) there are an adequate number of research participants suitable to be approached for enrolment for this study

( ) Yes ( ) No (•) Not applicable

d) this population is not being excessively recruited for clinical research

( ) Yes ( ) No (•) Not applicable

e) This Qualified Investigator is entitled to provide health care under the applicable laws and he/she is a member in good standing with his/her respective regulatory authority. The Qualified Investigator is qualified to perform the proposed clinical trial.

( ) Yes ( ) No (•) Not applicable (for non-regulated investigations)

Please obtain signature from Division head. Department head signature should be obtained only when the Division head is unavailable or when the Principal Investigator for the application is a Division head.

Name: Guy Hebert

Contact Number:

Please Note: Separate copies of Section 23 should be signed by all administrators who have signing authority over the financial cost centre(s) affected by the research study. These would include Administrative Directors of: 1) the clinical program(s) where the research is sited and 2) departments/services/programs that will provide significant services (e.g. Department of Health Records for a chart review study).

Ottawa Hospital Research Institute
Institut de recherche de l'Hôpital d'Ottawa

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UNIVERSITY OF OTTAWA HEART INSTITUTE
INSTITUT DE CARDIOLOGIE DE L'UNIVERSITÉ D'OTTAWA

Ottawa Health Science Network Research Ethics Board/ Conseil d'éthique de la recherche du Réseau de science de la santé d'Ottawa

January 5, 2017

Dear Dr. Thiruganasambandamoorthy:

RE: Protocol# - 20150648-01H **Derivation of a Clinical Decision Tool for Predicting Adverse Outcomes among Emergency Department Patients with Lower Gastrointestinal Bleeding**

Renewal Expiry Date - January 4, 2018

Thank you for the submission of the Annual Renewal Report dated December 08, 2016 and for your e-mail of January 05, 2017. I am pleased to inform you that your Annual Renewal Request was reviewed by the Ottawa Health Science Network Research Ethics Board (OHSN-REB) and is approved. No changes, amendments or addenda may be made in the protocol or the consent form without the OHSN-REB's review and approval.

Also approved is:
-Study end date extended to December 31, 2017

Renewal is valid for a period of one year. Approximately two months prior to that time, a single renewal form should be sent to the REB office.

OHSN-REB complies with the membership requirements and operates in compliance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans; the International Conference on Harmonization - Good Clinical Practice: Consolidated Guideline; and the provisions of the Personal Health Information Protection Act 2004.

Yours sincerely,

RESEARCH AGREEMENT
FREEDOM OF INFORMATION AND PROTECTION OF PRIVACY

THIS AGREEMENT is made between:

HER MAJESTY THE QUEEN IN RIGHT OF THE PROVINCE OF ONTARIO
as represented by

The Ministry of Community Safety and Correctional Services

Office of the Chief Coroner
(hereinafter referred to as the "Institution")

– and –

Ottawa Hospital Research Institute (OHRI)
(hereinafter referred to as the "Researcher")

WHEREAS Venkatesh Thiruganasambandamoorthy of the Ottawa Hospital is the principal investigator (PI) for this research project;

AND WHEREAS the Researcher has indicated interest in researching deaths related to a lower gastrointestinal bleed;

AND WHEREAS the Researcher is interested in researching the incidence of such effects for the years 2013-2014;

AND WHEREAS the Researcher has indicated that the purpose of his/her research is to derive a clinical decision tool for predicting adverse outcomes among emergency department patients with lower gastrointestinal bleeding;

AND WHEREAS, in order to conduct their research, the Researcher has requested access to records that are in the custody and under the control of the Institution;

NOW THEREFORE the Researcher understands and promises to abide by the following terms and conditions:

1. The Researcher acknowledges that he/she will have access only to the completed records or files provided to them by the Office of the Chief Coroner (OCC), as a branch of the Institution.

2. The Researcher undertakes not to seek or obtain copies of material or files made available to him/her by the Institution.

Journals: Ethical Considerations in the Conduct and Reporting of Research: Authorship and Contributorship (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html).

The nature of the OCC/OFPS staff members' participation as an author (or not) should be mutually agreed upon before the research is commenced. In certain research, the role may evolve, in which discussions regarding authorship should occur at the earliest time this evolution is recognized.

14. Upon review and discussion of the draft final report, if any, by the Institution, the Researcher shall consider the representations of the Institution prior to finalizing the final report. **The Researcher shall provide a final report to the Institution upon completion and forward a copy of all publications arising from data obtained from the Office of the Chief Coroner.**

15. The Researcher shall keep the information in a physically secure location to which access is given only to the Researcher. The Institution reserves the right to inspect such location, at any time. The Researcher consents to inspection by the Institution at any time of the location where the information is stored.

16. The Researcher shall not contact any individual to whom personal information relates, or the next of kin of such individual, directly or indirectly, without the prior written authority of the Institution.

17. The Researcher agrees to pay all costs incurred by the Institution under this Agreement.

18. The Researcher agrees that any method of secure transportation of the data is subject to the approval of the Institution.

19. The Researcher agrees to indemnify the Institution, its employees and agents, against all costs, losses, expenses and liabilities incurred as a result of a claim or proceedings related to this Agreement, unless it was caused by the negligence or willful act of an employee of the Institution while acting within the scope of his or her employment.

20. The Researcher agrees to abide by the provisions of Copyright law in the performance of their obligations under this Agreement.

The Researcher further agrees to indemnify the Institution, its employees and agents, against all costs, losses, expenses and liabilities incurred as a result of a claim or proceeding resulting from a breach of Copyright law.

21. Notices under this Agreement shall be in writing and sent by personal delivery, or by ordinary prepaid mail.

Acknowledgement

Having read this Agreement, I hereby agree to act in accordance with all terms and conditions herein.

SIGNED 21 day of, January 2016

DATE:

Dr. J. Edwards
Regional Supervising Coroner
Central Region – Toronto East Office
Position: Chair, Research Committee
Pursuant to delegated authority
Branch: Office of the Chief Coroner for Ontario

January 5, 2015

Dear Dr. Thiruganasambandamoorthy,

Re: Support of Research Project (REB Protocol # 20150648-01H)

This letter is to advise you that, once a research agreement has been signed by both parties, the Office of the Chief Coroner will provide you with access to Ontario death investigation data in order to support your project entitled **Derivation of a Clinical Decision Tool for Predicting Adverse Outcomes among Emergency Department Patients with Lower Gastrointestinal Bleeding**.

It would be appreciated if you would ensure that our office is acknowledged in your report. In addition, we would like to receive a copy of your report for our records, once it is completed.

Regards,

Queensway Carleton Hospital

April 15, 2016

Dr. Rosa Ramaekers
1053 Carling Avenue
Ottawa, ON K1Y 4E9

RE: **Study 16-01:** Derivation of a Clinical Decision Tool for Predicting Adverse Outcomes among Emergency Department Patients with Lower Gastrointestinal Bleeding

Dear Dr. Ramaekers:

Thank you for your submission of the application for approval regarding the above named study. I am pleased to inform you that your study has been approved, and this will extend to March 31st, 2017. We request that two months prior to that date you submit a Protocol Continuing Review Form at which time you may request an extension of approval if so indicated. We also require an End-of-Study Report to be submitted as soon as possible from the date of completion or termination of your research. The REB requires Investigators to comply with the guidelines described in the Tri-Council Policy Statement (2010): Ethical Conduct for Research Involving Humans –TCPS-2, as well as other regulatory standards for research practice in Ontario/Canada which are pertinent to your study.

Please note that you are required to request approval from the QCH REB for any and all modifications by which you plan to amend your protocol. We do require, as well, that you inform the QCH REB of any complaints made by participants in the study, *or agents of those participants*, within 7 days of having received the complaint. Should you have any questions I should be happy to discuss them with you.

Thank you and should you have any questions, please do not hesitate to contact me.

Sincerely,

To Whom It May Concern:

This letter is to inform you that the REB team will have access to patient charts and all patients information will be held confidential.

Any questions or concerns you can call the office at

Thanks,

Hôpital Montfort

Un hôpital d'enseignement affilié à l'Université d'Ottawa

A teaching hospital affiliated with the University of Ottawa

Avis d'approbation éthique
Comité d'éthique de la recherche (CÉR) de l'Hôpital Montfort

Le 4 mars 2016

Chercheur principal :

Dr Venkatesh Thiruganasambandamoorthy
Hôpital d'Ottawa
Department of Emergency Medecine

Co-chercheur

Dr Jeffrey Perry
Hôpital d'Ottawa, Emergency Medecine
Institut de recherche de l'Hôpital d'Ottawa

Chercheur assistant

Rosa Ramaekers
Hôpital d'Ottawa
Department of Emergency Medecine

Titre du projet : « Derivation of a clinical decision tool for predicting adverse outcomes among Emergency Department patients with Lower Gastrointestinal Bleeding »

Numéro du dossier : VT-09-02-16

Date de début : 4 mars 2016

Date de fin : 3 mars 2017

En conformité avec l'Énoncé de politique des trois conseils — Éthique de la recherche avec des êtres humains (ÉPTC 2), décembre 2014, le Conseil canadien des normes, les bonnes pratiques cliniques : directives consolidées, Conférence internationale sur l'harmonisation des exigences techniques relatives à l'homologation des produits pharmaceutiques à usage humain (ICH-GCP E6), la Loi de 2004 sur la protection des renseignements personnels sur la santé, les lois et règlements applicables en Ontario, je confirme que le Comité d'éthique de la recherche (CÉR) de l'Hôpital Montfort a évalué et approuvé votre projet de recherche et les documents suivants pour les dates de début et de fin mentionnées ci-dessus :

- Protocole de recherche, version 4, datée de novembre 2015
- Clinical decision tool for Lower Gastrointestinal Bleeding Case Record Form, version datée du 1er octobre 2015

Le CÉR de l'Hôpital Montfort est constitué et exerce ses activités d'une manière conforme à la Loi sur les aliments et les drogues, la Partie C, Titre 5, du Règlement sur les aliments et drogues et aux règlements applicables, la partie 4 du Règlement sur les produits de santé naturels; partie 3 du Règlement sur les instruments médicaux ainsi qu'au « Codes of Federal Regulations » des États-Unis.

Le protocole de l'étude ne peut être modifié sans une approbation préalable du CÉR sauf s'il est question de la sécurité immédiate des participants. Vous devez aviser le CÉR immédiatement de tout changement, événement indésirable ou nouvelle information pouvant augmenter le risque de l'étude, modifier le cours de l'étude ou atteindre la sécurité des participants. Les modifications au projet et aux outils de recrutement doivent être soumises au CÉR.

Veuillez nous acheminer **quatre semaines avant la date d'échéance de cet avis d'approbation**, un rapport final afin de fermer le dossier ou de faire une demande de renouvellement du certificat d'approbation éthique de l'étude.