Timing of Upper Endoscopy Influences Outcomes in Patients With Acute Nonvariceal Upper GI Bleeding

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Student Name: Aaron J. Cohen, B.S.

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Mentor Name(s) and Affiliations: John R. Saltzman, MD, Division of Gastroenterology, Brigham and Women's Hospital

Abstract

TITLE: Timing of upper endoscopy influences outcomes in patients with acute nonvariceal upper GI bleeding

Aaron Cohen, Navin Kumar, Jennifer Nayor, Brian Claggett, and John Saltzman

Purpose: Upper endoscopy performed within 24 hours is a mainstay of treatment in patients with an upper gastrointestinal bleed (UGIB). Despite this, the role for more urgent endoscopy (within 12 hours) is unclear. This study aimed to assess whether patients presenting with high-risk or lower-risk UGIB, as defined by established risk scores, have different outcomes with urgent vs. non-urgent endoscopy.

Methods: A retrospective study of 361 patients admitted to an academic hospital from 2004 to 2014 with nonvarcieal UGIB. Primary outcomes included a composite of inpatient death, inpatient rebleeding, need for surgical or interventional radiologic intervention, or endoscopic reintervention. For each patient, the Glasgow-Blatchford score (GBS) was calculated, with lower-risk defined as a GBS < 12, and high-risk defined as a GBS > 12. Time to endoscopy was defined as the time from arrival in the emergency department to the procedure start time for the initial endoscopy.

Results: Of the 361 patients, the mean age was 64 years and the mean GBS was 9.5. The median time to endoscopy was 20.8 hours with 223 patients (62%) undergoing endoscopy within 24 hours and 89 patients (25%) within 12 hours. 37 patients (10%) experienced the primary outcome. Patients who underwent urgent endoscopy within 12 hours had an increased risk of reaching the composite outcome compared to patients who underwent non-urgent endoscopy (OR 5.6; 95% CI 2.8-11.4; $p<0.001$). In the lower-risk group (GBS <12), patients who underwent urgent endoscopy were more likely to reach the composite outcome (OR 0.71 per 6 hours; 95% CI 0.55-0.91; $p=0.008$). In high-risk patients (GBS >12), time to endoscopy did not predict the composite outcome (adjusted OR 0.93 per 6 hours; 95% CI 0.77-1.13; $p=0.47$).

Conclusions: In a cohort of patients presenting with non-variceal UGIB, urgent endoscopy significantly predicts worse outcomes in lower-risk patients when compared with non-urgent endoscopy. In high-risk patients, time to endoscopy is not a significant predictor of worse outcomes.

A. Student contribution

I worked on this project alongside Dr. Navin Kumar, a gastroenterology fellow at BWH, and Dr. John Saltzman, a gastroenterology attending at BWH. Dr. Saltzman conceived the idea for the project and determined the research approach with Dr. Kumar. In the initial planning stages, I worked with Dr. Kumar on determining the best approach to building our patient database and deciding what variables we would want to include. I met frequently with him to discuss ideas for the project and help determine what our primary and secondary outcomes should be. One notable example was my suggestion that we only include endoscopic re-intervention and not endoscopic intervention as an outcome, as the latter merely reflects the disease process at hand.

My main work on the project involved construction of the patient database. I took the lead on this aspect of the project. Between Dr. Kumar and I, we reviewed 361 patient charts. For each patient, I determined key demographics, clinical co-morbidities, date/time of admission and endoscopy, risk score totals, and a variety of primary or secondary outcomes. The completion of this task took over 200 hours and led to a database that can be used for multiple studies. Besides reviewing charts, I also met frequently with Dr. Kumar to ensure that we defined certain outcomes very specifically and in the same manner to ensure consistency.

After construction of the database, I aided in the writing of the manuscript. Since I spent the majority of my time working on chart reviews, I was responsible for writing the methods section of the paper. I also helped with the final review of the manuscript prior to submission.

Dr. Navin Kumar was responsible for writing the remainder of the manuscript as well as working with the statistician, Dr. Brian Claggett, on analyzing the data. Dr. John Saltzman served as the principal investigator and provided intellectual contributions at all stages of the project.

B.

Upper gastrointestinal bleeding (UGIB) is defined as any bleeding that occurs from the mouth to the proximal duodenum. UGIB is commonly divided into variceal bleeding or non-variceal bleeding (NVUGIB). Annually, UGIB accounts for nearly 300,000 hospitalizations per year, with an approximate 5% mortality rate. [1]

The initial management of NVUGIB is largely agreed upon, and consists of upfront fluid resuscitation with 2 large-bore IV access and vital sign monitoring. Proton pump inhibitor therapy is also administered early in the management. [2] Blood transfusions, which in the past were administered liberally, are now shown to be more beneficial when given restrictively. Based on data from a large randomized-controlled trial, blood transfusions should typically be given when the patient's hemoglobin falls below 7 g/dl. [3] Per consensus guidelines, patients should also undergo risk stratification at presentation, using validated prognostic scores such as the Glasgow Blatchford Score (GBS) or AIMS65 score. [4,5]

Upper endoscopy is a hallmark in the management of NVUGIB both for diagnosis and treatment purposes. Current guidelines recommend that patients presenting with NVUGIB undergo endoscopy within 24 hours of admission. [6] Given the benefit of endoscopy performed within 24 hours, questions naturally arose if there was any benefit to even more urgent endoscopy. A retrospective study found that patients presenting with NVUGIB who underwent endoscopy within 8 hours showed no improvements in mortality or recurrent bleeding rates compared with patients who underwent endoscopy in the 8-24 hour window. [7] Another similar study compared outcomes between patients who received endoscopy immediately in the ER with those who received it within 24 hours. The emergent endoscopy group received an endoscopy on average in 2.1 hours from admission while the delayed group received an endoscopy in an average of 12.0 hours from admission. Despite similar patient characteristics, early endoscopy did not lead to an improvement in recurrent bleeding, medical complications, the need for surgery, or length of stay.[8] A randomized-controlled trial that randomized patients with NVUGIB to either urgent (before hospitalization in the emergency room) or elective (after admission) endoscopy showed that urgent endoscopy again did not reduce hospitalization or resource utilization. [9]

Given the studies showing a paucity of benefit for urgent endoscopy, the question arose of whether there may be a benefit to urgent endoscopy in selected higher-risk patients. A study of 934 patients at a tertiary medical center sought to address this question. The authors evaluated all patients

undergoing EGD for a presumed UGIB over an 18 month period, and included both variceal and non-variceal causes of bleeding. The major finding was that in high-risk patients (GBS>12), presentation to endoscopy time was longer in patients who died compared to those who survived. The effect was maximized using a cutoff time of 13 hours from presentation. Interestingly, zero patients in the less than 13 hours group died during the admission. One possible confounder is that patients who died during admission may be inherently different than those who survived. For example, endoscopy may have been delayed in patients who were critically ill and needed additional resuscitation. However, the authors did note that there was a similar percentage of high-risk endoscopic lesions in the group that died compared with the group that survived, which suggested a similar severity of bleeding. In addition, their multivariate analysis accounted for the presence of several comorbidities. Of note, the benefit of urgent endoscopy was not seen in lower-risk patients (GBS <12). Based on this study, the authors concluded that there may be a mortality benefit to urgent endoscopy in high-risk UGIB patients. [10] To our knowledge, no further studies have evaluated the timing of endoscopy in NVUGIB based on bleeding prognostic scores.

Given the unsettled question of the benefit of urgent endoscopy, our study aimed to evaluate the relationship between the timing of endoscopy and outcomes in patients presenting to an academic medical center. Our goal was to assess whether high-risk vs lower-risk patients have different outcomes depending on the rapidity of endoscopy. Using a retrospective approach, we built a database of 361 patients who presented with non-variceal UGIB from 2004-2014, and assessed a variety of clinical outcomes as well as the time from presentation to endoscopy.

Our findings demonstrated that time to endoscopy was a significant predictor of reaching a composite outcome including death, inpatient rebleeding, endoscopic reintervention, or need for surgical or interventional radiological (IR) intervention. Specifically, patients undergoing urgent endoscopy within 12 hours of admission had a greater than 5-fold increased risk of reaching our primary outcome compared with patients undergoing non-urgent endoscopy after 12 hours. When stratified by the risk of the patient and after controlling for multiple factors on multivariate analysis, urgent endoscopy remained a significant predictor of worse outcomes in the lower-risk group only.

Our study is consistent with previous studies that demonstrate no difference in mortality between urgent and non-urgent endoscopy. [7,8] While prior studies have focused on the lack of benefit to early endoscopy, our study is the first to show potential harm in taking patients urgently to endoscopy. Interestingly, this finding was driven by differences in outcomes in the lower-risk group and not in

the high-risk group. One hypothesis for this finding is that lower-risk patients may appear well on presentation and thus may receive inadequate resuscitation prior to undergoing endoscopy. Further studies are needed to ascertain whether or not lower-risk patients receive adequate resuscitation. Interestingly, our results contrast with the findings in Lim et al., which demonstrated that high-risk patients benefited from early endoscopy. [10]

Our findings provide further evidence that rushing patients to endoscopy may not provide any benefit to the patient and may in fact provide harm, particularly in lower-risk patients. Providers should ensure that patients are adequately fluid resuscitated and medically optimized prior to endoscopy. This has important implications for staffing and hospital management of NVUGIB. It may not make clinical sense to call in gastroenterology specialists overnight to perform an urgent endoscopy given the lack of benefit and potential harm of urgent endoscopy, particularly in lower-risk patients. While certain clinical scenarios will still prompt an emergent endoscopy (i.e. hemodynamic instability), house staff should be aware of this potential lack of benefit of urgent endoscopy for lower-risk patients, and should calculate a bleeding prognostic score for all patients with NVUGIB to help guide decision-making.

An important limitation to our work includes the retrospective nature of our study. Patients were not prospectively randomized to either urgent or non-urgent endoscopy and thus there may be important between group differences. Despite controlling for potential confounders, including Charlson comorbidity index, vital signs, and platelet count/INR, there may be differences in the groups that we were unable to account for. However, the mean GBS was not significantly different in the urgent and non-urgent groups, which suggests that the severity of bleeding was similar between the two groups.

While the use of a composite outcome may be a better reflection of overall patient outcomes in UGIB when compared with just the use of mortality, our study showed no significant difference in mortality between the urgent and non-urgent groups. In our cohort, mortality was low at 2% (although consistent with recent nationwide data) and thus our study was not significantly powered to detect a between group difference.[2]

Going forward, prospective, randomized studies need to be performed to determine if risk scores can be used to triage patients with UGIB to the optimal timing of endoscopy. For now, our findings emphasize the importance of adequate medical therapy prior to endoscopy.

In addition, we recently had an additional manuscript accepted with minor revisions. Using the same database, we show that an increase in BUN 24 hours after admission is a significant solitary predictor of mortality and reaching our composite outcome. This further strengthens the hypothesis that under resuscitation may contribute to poor outcomes in NVUGIB.

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Appendix: Published Manuscript

Kumar, N.K., Cohen, A.J., Nayor, J., Claggett, B., Saltzman, J.R. Timing of upper endoscopy influences outcomes in patients with acute nonvariceal upper GI bleeding. *Gastrointestinal Endoscopy.* 2016. In press

ABSTRACT

Background: Current guidelines advise that upper endoscopy be performed within 24 hours of presentation in patients with acute nonvariceal upper gastrointestinal bleeding (UGIB). However, the role of urgent endoscopy (< 12 hours) is controversial.

Aim: To assess if patients admitted with acute nonvariceal UGIB with lower- vs. high-risk bleeding have different outcomes with urgent compared to non-urgent endoscopy.

Methods: A retrospective cohort study was conducted of patients admitted to an academic hospital with nonvariceal UGIB. The primary outcome was a composite of inpatient death from any cause, inpatient rebleeding, need for surgical or interventional radiologic intervention, or endoscopic re-intervention. The Glasgow-Blatchford score (GBS) was calculated; lower-risk was defined as a GBS of < 12 and high-risk was defined as a GBS of ≥ 12.

Results: There were 361 patients including 37 patients (10%) who experienced the primary outcome. Patients who underwent urgent endoscopy had a greater than 5-fold increased risk of reaching the composite outcome (unadjusted OR 5.6; 95% CI 2.8-11.4; p<0.001). Lower-risk patients who were taken urgently to endoscopy were more likely to reach the composite outcome (adjusted OR 0.71 per 6 hours; 95% CI 0.55-0.91; p=0.008). However, in the high-risk patients, time to endoscopy was not a significant predictor of the primary outcome (adjusted OR 0.93 per 6 hours; 95% CI 0.77-1.13; p=0.47; adjusted p for interaction = 0.039).

Conclusion: Urgent endoscopy is a predictor of worse outcomes in select patients with acute nonvariceal upper gastrointestinal bleeding.

INTRODUCTION

Acute nonvariceal upper gastrointestinal bleeding (UGIB) is a common cause of hospital admission, accounting for nearly 300,000 hospitalizations annually in the United States alone (1) and a mortality rate of 2-14% (2-4). The initial management of patients with UGIB includes fluid resuscitation, hemodynamic monitoring, proton pump inhibitor therapy, management of anti-thrombotics, and blood transfusion for some patients (5). For the next step in management, current guidelines recommend that upper endoscopy be performed within 24 hours of presentation (6-9). However, the role of urgent endoscopy (i.e. within 12 hours) is controversial. Previous studies have shown that urgent endoscopy leads to increased detection of high-risk bleeding lesions and endoscopic therapy, without any improvement in clinical outcomes such as death, rebleeding or need for surgery (10-12). However, these studies did not stratify by bleeding severity and thus it is unclear if timing of endoscopy predicts outcomes in a high-risk population.

Lim et al. performed a retrospective study on the timing of endoscopy based on a bleeding prognostic score, and found that patients with high-risk bleeding, defined by a Glasgow-Blatchford score (GBS) ≥ 12, had a significantly lower mortality rate when taken urgently to

endoscopy (13). The authors concluded that patients with high-risk bleeding prognostic scores benefit from earlier endoscopy.

We aimed to evaluate the relationship between timing of endoscopy and clinical outcomes in patients presenting to a university hospital with UGIB and assess if patients with lower- vs. high-risk bleeding have different outcomes with urgent compared to non-urgent endoscopy.

METHODS

Study cohort

The research patient data registry (RPDR) is a centralized clinical data registry, which gathers and stores data from various electronic health record systems in the Partners Healthcare network. The RPDR was used to identify patients at the Brigham and Women's Hospital who were seen in the emergency department and subsequently admitted to the hospital between the years of 2004-2014. Any patients who were transferred from an outside hospital were not included in the study. The initial query was limited to those patients that presented with a principal ICD-9 diagnosis code for upper gastrointestinal bleeding (appendix). The search was further limited to cases with discharge summaries entitled "Upper Gastrointestinal Bleed" or "UGIB," which yielded 432 patients. Of these, patients were excluded if there was a variceal source of UGIB (n=26) or if endoscopy was not performed during the admission (n=41). Patients were also excluded if they had a non-endoscopic intervention for hemostasis prior to upper endoscopy (n=1), or if endoscopy had been performed as an outpatient within 7 days prior to hospital admission (n=3) for a final cohort of 361 patients. This study was reviewed and approved by the institutional review board of Partner's Healthcare.

Data collection

From this dataset, two independent reviewers (NLK, AJC) screened the medical record (electronic and paper chart) including discharge summaries and related notes, labs, and endoscopy reports to confirm that each case represented a true upper gastrointestinal bleed. If

a patient was admitted more than once during the study period for an upper gastrointestinal bleed, the earliest (or index upper gastrointestinal bleeding) visit was included in the analysis.

Data was collected on demographics, relevant past medical history and medication use. Patients receiving warfarin, therapeutic enoxaparin or therapeutic fondaparinux were classified as receiving any anticoagulation. No patients in the study sample were taking any of the direct oral anti-coagulants. Emergency department data (i.e. initial vital signs and laboratory values) was also collected to calculate the GBS and AIMS65 scores, which are two extensively studied prognostic scores that can be calculated at initial presentation and are predictive of poor outcomes in UGIB (14, 15). Given that the GBS is more widely known and was used in the earlier literature, we decided to use the GBS to stratify the study sample. Patients with a GBS of < 12 were considered lower-risk (n= 240) and those with a GBS ≥ 12 were considered high-risk (n= 121). Co-morbid conditions identified through medical chart review were also obtained and a Charlson comorbidity index (CCI) was calculated for each patient.

Timing of Endoscopy

For each patient included in the database, the time and date of emergency department arrival was obtained from the hospital billing record. In addition, the date of initial endoscopy was obtained from the medical record and the time of endoscopy was obtained from the electronic endoscopy scheduling system or endoscopy procedure report. Time to endoscopy was defined as the time interval from emergency department arrival to the procedure start time for the initial upper endoscopic examination. If a patient presented to the emergency department after

3 PM on the day prior to a holiday or weekend day, the patient was identified as a holiday/weekend admission given that the endoscopy unit would be closed on the subsequent day. However, urgent endoscopy was available 24/7 to be performed in the emergency department or intensive care units (ICU) based on the on-call gastroenterologist's decision.

Outcome assessment

The primary composite outcome for the study was inpatient death from any cause, inpatient rebleeding, need for surgical or interventional radiologic intervention, or endoscopic re-intervention. The medical chart was then reviewed for the entirety of the hospitalization to assess for the development of any of these five clinical outcomes. Inpatient rebleeding after the initial endoscopy was defined as fresh hematemesis or blood passing from a nasogastric tube, fresh melena or hematochezia with accompanying laboratory (hemoglobin drop of greater than 2 g/dL within 24 hours) or vital sign changes (systolic blood pressure decrease to less than 100 mm Hg or heart rate increase to greater than 100 beats/min) to indicate active bleeding, or rebleeding demonstrated on endoscopy, bleeding scan, or angiography. Endoscopic re-intervention was defined as a repeat endoscopy with intervention performed for the purpose of hemostasis. Secondary outcome data were also recorded including whether an endoscopic intervention was performed on initial upper endoscopy, length of stay, or blood transfusion (need for transfusion and the total units of blood transfused).

Statistical Analysis

Patient characteristics were summarized using means and standard deviations or median and interquartile range for continuous variables and counts and percentages for categorical variables. Baseline characteristics between subgroups of patients were compared using t-tests and Pearson's chi-squared test for continuous and binary variables, respectively. Univariate associations between patient characteristics and the composite outcome were assessed and described using odds ratios from logistic regression models. Multivariable analyses were conducted through the use of forward stepwise selection procedures with p-value threshold of 0.05. The variables considered for inclusion in the multivariable analysis were as follows: age, gender, weekend/holiday presentation, aspirin, thienopyridine, warfarin, any anticoagulation, CCI, systolic blood pressure, heart rate, platelet count, INR, AIMS65 score, GBS, and timing of endoscopy. P-values less than 0.05 were considered significant. All analyses were conducted using STATA version 14 (College Station, TX).

RESULTS

Patient characteristics

There were 361 patients included in the study cohort, with 89 patients (25%) receiving urgent endoscopy and 272 patients (75%) receiving non-urgent endoscopy. Table 1 shows the patient characteristics according to timing of endoscopy. The mean age, gender, and presentation on a weekend or holiday were not significantly different between the two groups. Patients receiving non-urgent endoscopy were more likely to be receiving a thienopyridine (14% vs. 6%; p=0.035) or warfarin (18% vs. 9%; p=0.036), whereas patients receiving urgent endoscopy were more likely to have lower systolic blood pressures (104 vs. 120 mm Hg; p<0.001) and elevated heart rates (96 vs. 90; p=0.007) on presentation. Patients undergoing urgent endoscopy also had elevated GBS (10.5 vs. 9.1; p=0.004) and AIMS65 scores (1.3 vs. 1.0, p=0.008), and underwent endoscopy sooner after presentation (5.5 vs. 24.1 hrs; p<0.001).

Overall patient outcomes

There were 37 patients (10%) that experienced one or more components of the primary composite outcome: 8 died (2%), 20 rebled (6%), 5 required surgery (1%), 8 required interventional radiology (2%), and 13 needed repeat endoscopic intervention after the initial upper endoscopy (4%). All deaths occurred after the initial upper endoscopy was performed. In terms of secondary outcomes, 102 patients (28%) underwent an endoscopic intervention and 280 patients (78%) received a blood transfusion during the hospital stay. The mean number of

red blood cell units transfused per patient was 3.3 (SD ± 4.1). The mean length of stay was 4.0 days (SD ± 4.0).

Timing of endoscopy and other predictors of the composite outcome

On univariate analysis (Table 2), time to endoscopy was a significant predictor of the composite outcome (OR 0.77; 95% CI 0.66-0.91; p=0.002), with a 23% reduced risk of reaching the composite outcome with increased time to endoscopy (per 6 hour interval). For every 10 mm Hg increase in systolic blood pressure, there was a 22% reduced risk of reaching the composite outcome (OR 0.78; 95% CI 0.67-0.90; p=0.001). The only other covariate that reached statistical significance was the AIMS65 score (OR 1.68; 95% CI 1.21-2.32; p=0.002), with each additional point conveying an increase of 68% in the odds of reaching the composite outcome. All other covariates, including patient demographics, medication use, and presence of thrombocytopenia or coagulopathy, were not significant predictors.

On multivariate analysis (Table 2), time to endoscopy remained a significant predictor of the composite outcome (adjusted OR 0.81 per 6 hours; 95% CI 0.69-0.94; p=0.005), with increased time to endoscopy having a reduced odds of reaching the composite outcome. Systolic blood pressure also remained a significant predictor (adjusted OR 0.82 per 10 mm Hg; 95% CI 0.70-0.95; p=0.008) in this model. Patients admitted on a weekend or holiday had a greater than 2-fold odds of reaching the composite outcome (adjusted OR 2.27; 95% CI 1.05-4.87; p=0.036).

When restricting the multivariate analysis to only those patients who received endoscopy within 24 hours, time to endoscopy remained a significant predictor of the composite outcome (adjusted OR 0.55 per 6 hours; 95% CI 0.37-0.80; p=0.002).

Urgent vs. non-urgent endoscopy

The time to endoscopy threshold with the most significant odds ratio of reaching the composite outcome was 12 hours. Patients who underwent urgent upper endoscopy within 12 hours had a greater than 5-fold risk of experiencing the composite outcome than those patients who underwent non-urgent upper endoscopy after 12 hours (OR 5.6; 95% CI 2.8-11.4; p<0.001). Table 3 shows the distribution of outcomes in patients undergoing urgent vs. non-urgent endoscopy. Patients who received urgent upper endoscopy were more likely to rebleed (11% vs. 4%; p=0.007), require surgical (4% vs. 0%, p=0.004) or interventional radiology intervention (6% vs. 1%; p=0.012), or need repeat endoscopic intervention (10% vs. 1%; p<0.001). Endoscopic interventions (39% vs. 25%; p=0.008) and need for transfusion (85% vs. 75%; p<0.001) were also significantly higher in the urgent vs. non-urgent group.

Timing of endoscopy in lower-risk patients (GBS of < 12 points)

There were 240 patients (66%) with lower-risk bleeding of which 23 patients (10%) reached the primary outcome. On univariate analysis (Table 4), time to endoscopy was again statistically significant (OR 0.64 per 6 hours; 95% CI 0.49-0.83; p=0.001) with a decreased odds of reaching

the composite outcome with increased time to endoscopy. Systolic blood pressure (OR 0.77 per 10 mm Hg; 95% CI 0.64-0.93; p=0.006) and therapeutic anticoagulation (OR 3.60; 95% CI 1.4-9.27; p=0.008) were also significant predictors in the univariate analysis.

On multivariate analysis (Table 4), time to endoscopy remained a significant predictor of the composite outcome in the lower-risk patients (adjusted OR 0.71 per 6 hours; 95% CI 0.55-0.91; p=0.005). When comparing the lower-risk patients who underwent urgent endoscopy (48 patients; 20%) vs. non-urgent endoscopy (192 patients; 80%), the urgent group was more likely to reach the composite outcome (29% vs. 5%; p<0.001), rebleed (10% vs. 3%; p=0.015), require surgical (6% vs. 1%; p=0.006) or interventional radiology intervention (2% vs. 1%; p=0.042), and/or need repeat endoscopic intervention (12% vs. 1%; p<0.001). The mean GBS for the urgent vs. non-urgent endoscopy groups was not significantly different (7.5 vs. 7.2; p=0.51). The percentage of lower-risk patients receiving blood transfusion also did not differ between the urgent and non-urgent endoscopy groups (75% vs. 65%; p=0.19).

Timing of endoscopy in high-risk patients (GBS of ≥ 12 points)

There were 121 patients (34%) with high-risk bleeding of which 14 patients (12%) reached the primary outcome. On univariate analysis (Table 5), systolic blood pressure was a significant predictor of the composite outcome (OR 0.73 per 6 hours; 95% CI 0.54-0.98; p=0.035). Presentation on a weekend or holiday was also statistically significant (OR 4.35; 95% CI 1.37-

13.81; p=0.013), with a greater than 4-fold odds of reaching the composite outcome. Time to endoscopy, however, was not a significant predictor in the high-risk group (OR 0.94 per 6 hours; 95% CI 0.78-1.13; p=0.512).

On multivariate analysis (Table 5), both systolic blood pressure (adjusted OR 0.72 per 10 mm Hg; 95% CI 0.52-0.99; p=0.043) and presentation on a weekend or holiday (adjusted OR 4.22; 95% CI 1.29-13.9; p=0.018) remained statistically significant. Time to endoscopy was not significant in the multivariate analysis (adjusted OR 0.93 per 6 hours; 95% CI 0.77-1.13; p=0.47), and was significantly less prognostic in the high-risk patients compared to lower-risk patients (adjusted p for interaction = 0.039). When comparing the high-risk patients who underwent urgent (41 patients; 34%) vs. non-urgent (80 patients; 66%) upper endoscopy, there were no significant differences in the rates of reaching the composite outcome or the individual components of the composite outcome. The mean GBS for the urgent vs. non-urgent endoscopy groups was not significantly different (14.1 vs. 13.7; p=0.28). The percentage of high-risk patients receiving blood transfusion also did not differ between the urgent and non-urgent endoscopy groups (98% vs. 99%; p=0.63).

DISCUSSION

In this retrospective cohort study of 361 patients with an acute nonvariceal UGIB at an academic center, time to endoscopy was a significant predictor of reaching a composite clinical outcome of death, inpatient rebleeding, need for surgical or interventional radiology intervention, or repeat endoscopic intervention. Patients who underwent urgent endoscopy (within 12 hours) had a greater than 5-fold increased risk of reaching the composite outcome than patients who received non-urgent endoscopy (after 12 hours). In the subgroup analysis, urgent endoscopy was a significant predictor of worse outcomes in the lower-risk bleeding group only, and this finding persisted after accounting for multiple confounders.

Several studies have investigated the effect of endoscopy timing on clinical outcomes in acute nonvariceal UGIB, although the studies differed significantly in their designs. A retrospective study of 81 patients with UGIB from a peptic ulcer showed no difference in clinical outcomes (mortality, rebleeding, or surgery) or length of stay between patients receiving endoscopy within 3 hours vs. 48 hours, but there was a significantly increased rate of endoscopic therapy (77% vs 47%; p=0.006) and detection of high-risk bleeding (19% vs. 3%; p=0.022) in the emergent endoscopy group (10). In a randomized control trial of 93 patients with UGIB, there also was no difference in clinical outcomes or length of stay in the early endoscopy (within 6 hours) vs. elective endoscopy (within 48 hours) groups, although more high-risk endoscopic lesions were again identified in the early group (32% vs. 20%; p=0.017) (11). Similarly, a larger retrospective study of 189 patients compared patients receiving endoscopy within 8 hours vs.

between 8 and 24 hours and found no difference in mortality or recurrent bleeding despite an increased detection of high-risk ulcers with active bleeding (19% vs. 8%; p=0.03) or visible vessels (34% vs. 12%; p<0.01) and a corresponding increased need for endoscopic therapy (40% vs. 15%; p<0.001) in the early vs. later group (12). Thus these prior studies did not demonstrate a benefit from urgent endoscopy in patients presenting with an UGIB.

A large retrospective study of 909 patients from 13 different hospitals did find a decreased length of stay (5.0 vs. 6.4 days; p<0.001) in patients receiving endoscopy within 24 hours vs. after 24 hours (16). Similarly, a nationwide study with 2592 patients found that endoscopy performed within one day of presentation was associated with a significant decrease in length of stay (-1.95 days; 95% CI -1.29 to -2.60) and need for surgery (adjusted OR 0.37; 95% CI 0.21-0.66) (17). Current guidelines recommend proceeding with upper endoscopy for UGIB within 24 hours of presentation (6-9).

To assess if prognostic scores for UGIB could further inform the decision of when to perform upper endoscopy, Lim et al. conducted a retrospective study of 934 patients presenting with UGIB and stratified the analysis into lower-risk (GBS <12) and high-risk (GBS ≥ 12) groups (13). In the lower-risk group (837 patients; 90%), timing of endoscopy was not associated with inpatient mortality. However, in the high-risk group (97 patients; 10%), which comprised the minority of the study sample, timing of endoscopy was the only significant predictor of mortality (adjusted OR 1.09; 95% CI 1.02-1.17). All patients who received endoscopy within 13

hours survived, compared to a mortality rate of 44% if endoscopy was performed after 13 hours ($p<0.001$). However, there were no differences in other clinical outcomes related to UGIB such as need for transfusion, rebleeding, or need for surgery, which may suggest that the deaths in the group who had endoscopy performed after 13 hours were due to causes unrelated to UGIB.

Our findings are consistent with prior studies that did not demonstrate any difference in mortality from urgent vs. non-urgent endoscopy (10-12). However, in our study urgent endoscopy is associated with an *increased* risk of experiencing a composite outcome that included death in addition to inpatient rebleeding, need for surgery or interventional radiology, or repeat endoscopic intervention, which has previously not been reported in the literature. Although prior studies have consistently demonstrated the lack of benefit with more urgent endoscopy, ours is the first study to our knowledge that suggests potential harm in taking patients earlier to endoscopy. Our stratified analysis showed that this finding was driven by the lower-risk patients in our cohort, whereas timing of endoscopy was not a significant predictor of the composite outcome in high-risk patients. Although we cannot confirm this theory based on retrospective review, we hypothesize that lower-risk patients who are taken earlier to endoscopy may receive inadequate fluid resuscitation given that they appear more stable on presentation. This potential tendency to under-resuscitate during the critical early period of management is exacerbated when the patient is transported off the medical floor for an endoscopic procedure. Also it is important to note that the lower-risk patients in our study cohort had a mean GBS of 7.2, and thus should not be considered lowest-risk (i.e. GBS $\leq$ 2).

In contrast, high-risk patients are more likely to receive adequate fluid resuscitation and prompt proton-pump inhibitor therapy prior to endoscopy given that their UGIB presentations are more severe. It may be this general medical therapy as opposed to the timing of endoscopy that is most significant in preventing poor outcomes from UGIB. Our results do contrast with the findings of Lim et al., in which high-risk patients benefited from urgent endoscopy, although one important difference is that we did not include patients who were already hospitalized and then developed UGIB. Prior evidence does show that inpatients with UGIB have a higher mortality rate compared to patients admitted for UGIB, even after adjustment for possible confounders (18).

In this study, presentation on a weekend or holiday was also associated with an increased odds of reaching the composite outcome. This finding contrasts with recent nationwide studies that showed no increase in mortality for patients presenting with UGIB on the weekends vs. weekdays (19, 20). However, we were able to identify the exact time of presentation, as opposed to day of presentation, and thus more accurately capture the weekend or holiday effect. We also used a composite outcome, which increased our ability to capture differences in other measures of poor outcome including rebleeding or need for intervention. Lastly, our subgroup analysis showed the weekend or holiday effect was seen in our high-risk patients but not lower-risk patients, and previous nationwide studies have not been able to stratify the analysis by bleeding risk. This result persisted on multivariate analysis after controlling for such

factors as time to endoscopy, which suggests that other factors (e.g. hospital staffing) may be contributory. High-risk patients who present on a weekend or holiday warrant careful attention.

There are some important limitations to consider in this study. The major limitation is the potential for confounding by indication, which suggests that the patients who underwent more urgent endoscopy were different, or sicker, than the other patients in the study. It is possible that the emergency department notified the GI consultant earlier for patients who appeared more unstable, which led to earlier endoscopy for this group. However, we showed that the mean GBS was not significantly different in the urgent vs. non-urgent endoscopy groups in the lower-risk or high-risk categories. The percentage of patients receiving blood transfusion also did not differ in either the lower-risk or high-risk population between urgent and non-urgent groups, which again suggests a similar severity of bleeding. Further, we controlled for several potential confounders to address other potential differences between the two groups, including patient demographics, presentation on a weekend or holiday, Charlson comorbidity index, pertinent vital signs and individual platelet count or INR value. Another limitation was that we relied on existing medical records to measure the exposures and outcomes of interest. However, two independent researchers performed the chart review and returned to the paper chart to obtain any information that was not documented in the electronic health record. It is also worth noting that the GBS did not reach statistical significance in predicting the composite outcome. However, the GBS has been shown to best predict the need for blood transfusions,

which was not part of our composite outcome (21). Lastly, we used a composite outcome as the primary outcome in our study as we believe this composite outcome is a good clinical measure of clinical outcomes in patients with UGIB, as all five individual components of the composite outcome reflect poor outcomes in UGIB. We showed that four of those five individual outcomes (with the exception of inpatient death) were each significantly more likely to occur in urgent vs. non-urgent endoscopy.

We found that timing of upper endoscopy is a significant predictor of experiencing worse outcomes in acute nonvariceal upper gastrointestinal bleeding, with urgent endoscopy (within 12 hours) associated with a higher rate of reaching a composite clinical outcome than with non-urgent endoscopy (after 12 hours). Lower-risk patients had worse outcomes with urgent endoscopy, whereas timing of endoscopy was not a significant predictor in high-risk patients. Further prospective studies are needed to assess the role of prognostic scores for patients presenting with acute nonvariceal upper gastrointestinal bleeding in determining the optimal timing of endoscopy.

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Table 1:

Characteristic	Urgent Endoscopy	Non-Urgent Endoscopy	P-value
Number of patients	89	272	-
Demographics			
Age (years)	63 ± 16	64 ± 15	0.52
Gender (male)	48 (54%)	146 (54%)	0.97
Weekend/holiday presentation	23 (26%)	67 (25%)	0.82
Aspirin	34 (38%)	124 (46%)	0.22
Thienopyridine	5 (6%)	38 (14%)	0.035
Warfarin	8 (9%)	50 (18%)	0.036
Any anticoagulation	14 (16%)	57 (21%)	0.28
Charlson comorbidity index	2 [1, 3]	2 [1, 4]	0.15
Vital signs			
Systolic blood pressure (mm Hg)	104 ± 27	120 ± 27	<0.001
Heart rate (bpm)	96 ± 20	90 ± 20	0.007
Laboratory values			
Platelet count (x 10^3/mL)	270 ± 122	294 ± 127	0.12
INR	1.2 [1.1, 1.3]	1.1 [1.0, 1.3]	0.52
Prognostic scores			
AIMS65 score	1.3 ± 1.0	1.0 ± 0.9	0.008
Glasgow-Blatchford score	10.5 ± 4.1	9.1 ± 4.1	0.004
Endoscopy			
Time to endoscopy (hours)	5.5 [4.2, 7.9]	24.1 [19.5, 43.5]	<0.001

Characteristics of patients receiving urgent (≤ 12 hrs) vs. non-urgent (> 12 hrs) endoscopy

Proportions presented as percentages. Means and standard deviations (SD) presented as mean ± SD. Medians and interquartile range (IQR) presented as median ± IQR. This notation is used throughout.

Table 2: Univariate and multivariate analyses of predictors of the composite outcome

Predictor	Odds Ratio (95% CI)	P-value
Univariate Analysis		
Demographics		
Age (years)	0.98 (0.78-1.21)	0.825
Gender (male)	0.90 (0.46-1.78)	0.759
Weekend/holiday presentation	1.74 (0.84-3.58)	0.134
Aspirin	0.66 (0.33-1.36)	0.266
Thienopyridine	0.19 (0.02-1.40)	0.102
Warfarin	0.80 (0.30-2.14)	0.656
Any anticoagulation	1.60 (0.73-3.47)	0.238
Charlson comorbidity index	1.10 (0.96-1.26)	0.166
Vital signs		
Systolic blood pressure (mm Hg)	0.78 (0.67-0.90)	0.001
Heart rate (bpm)	1.17 (0.99-1.38)	0.072
Laboratory values		
Platelet count (x 10^3/mL)	1.00 (1.00-1.00)	0.507
INR	0.97 (0.75-1.26)	0.840
Prognostic scores		
AIMS65 score	1.68 (1.21-2.32)	0.002
Glasgow-Blatchford score	1.08 (0.99-1.17)	0.093
Endoscopy		
Time to endoscopy (hours)	0.77 (0.66-0.91)	0.002
Multivariate Analysis		
Weekend/holiday presentation	2.27 (1.05-4.87)	0.036
Systolic blood pressure (mm Hg)	0.82 (0.70-0.95)	0.008
Time to endoscopy (hours)	0.81 (0.69-0.94)	0.005

Table 3: Outcomes in patients receiving urgent (≤ 12 hrs) vs. non-urgent (> 12 hrs) endoscopy

Outcome	**Urgent endoscopy (n=89)**	**Non-urgent endoscopy (n=272)**	**P-value**
Primary outcome			
Composite outcome	22 (25%)	15 (6%)	<0.001
Components of primary outcome			
Inpatient death	4 (4%)	4 (1%)	0.09
Inpatient rebleeding	10 (11%)	10 (4%)	0.007
Surgical intervention	4 (4%)	1 (0%)	0.004
Interventional radiology intervention	5 (6%)	3 (1%)	0.012
Endoscopic re-intervention	9 (10%)	4 (1%)	<0.001
Secondary outcomes			
Endoscopic intervention	35 (39%)	67 (25%)	0.008
Transfused	76 (85%)	204 (75%)	<0.001
Number of units transfused (per patient)	4.6 ± 6.0	2.8 ± 3.1	<0.001
Length of stay	4.3 ± 4.2	4.0 ± 4.0	0.45

Table 4: Univariate and multivariate analyses of predictors of composite outcome in lower-risk GBS patients (n=240)

Predictor	**Odds Ratio (95% CI)**	**P-value**
Univariate analysis		
Demographics		
Age (years)	0.92 (0.71-1.20)	0.541
Gender (male)	1.11 (0.47-2.64)	0.812
Weekend/holiday presentation	0.99 (0.37-2.64)	0.985
Thienopyridine	0.37 (0.05-2.83)	0.336
Warfarin	1.78 (0.56-5.67)	0.333
Any anticoagulation	3.60 (1.40-9.27)	0.008
Charlson comorbidity index	1.17 (0.99-1.39)	0.071
Vital signs		
Systolic blood pressure (mm Hg)	0.77 (0.64-0.93)	0.006
Heart rate (bpm)	1.14 (0.92-1.41)	0.221
Laboratory values		
Platelet count (x 10^3/mL)	1.00 (0.99-1.00	0.369
INR	1.20 (0.91-1.58)	0.188
Endoscopy		
Time to endoscopy (hours)	0.64 (0.49-0.83)	0.001
Multivariate analysis		
Age (years)	0.69 (0.49-0.98)	0.038
AIMS65	3.14 (1.70-5.80)	<0.001
Time to endoscopy (hours)	0.71 (0.55-0.91)	0.008

Table 5: Univariate and multivariate analyses of predictors of composite outcome in high-risk GBS patients (n=121)

Predictor	**Odds Ratio (95% CI)**	**P-value**
Univariate analysis		
*Demographics**		
Age (years)	1.09 (0.72-1.67)	0.673
Gender (male)	0.63 (0.21-1.95)	0.427
Weekend/holiday presentation	4.35 (1.37-13.81)	0.013
Warfarin	0.20 (0.02-1.58)	0.126
Any anticoagulation	0.37 (0.08-1.76)	0.214
Charlson comorbidity index	0.98 (0.78-1.24)	0.893
Vital signs		
Systolic blood pressure (mm Hg)	0.73 (0.54-0.98)	0.035
Heart rate (bpm)	1.21 (0.91-1.60)	0.194
Laboratory values		
Platelet count (x 10^3/mL)	1.00 (1.00-1.00)	0.865
INR	0.47 (0.17-1.32)	0.153
Endoscopy		
Time to endoscopy (hours)	0.94 (0.78-1.13)	0.512
Multivariate analysis		
Weekend/holiday presentation	4.22 (1.29-13.9)	0.018
Systolic blood pressure (mm Hg)	0.72 (0.52-0.99)	0.043

* No patients in the high-risk group on a thienopyridine reached the composite outcome.

APPENDIX

Appendix: International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) codes used to screen for patients with potential upper gastrointestinal bleeding.

ICD-9-CM Code	Description
456.0	Esophageal varices with bleeding
456.20	Bleeding esophageal varices in diseases classified elsewhere with bleeding
530.7	Mallory-Weiss syndrome
530.82	Esophageal hemorrhage
531.00	Acute stomach ulcer with hemorrhage
531.40	Chronic stomach ulcer with hemorrhage
532.00	Acute duodenal ulcer with hemorrhage
532.40	Chronic duodenal ulcer with hemorrhage
533.00	Acute peptic ulcer with hemorrhage
533.40	Chronic peptic ulcer with hemorrhage
534.00	Acute marginal ulcer with hemorrhage
534.40	Chronic marginal ulcer with hemorrhage
535.01	Acute gastritis with hemorrhage
535.11	Atrophic gastritis with hemorrhage
535.21	Gastric mucosa hypertrophy with hemorrhage
535.31	Alcoholic gastritis with hemorrhage
535.41	Other specified gastritis with hemorrhage
535.51	Gastritis/duodenitis not otherwise specified with hemorrhage
535.61	Duodenitis with hemorrhage

537.83 Angiodysplasia of the stomach/duodenum with hemorrhage

578.0 Hematemesis

578.9 Gastrointestinal hemorrhage not otherwise specified