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ORIGINAL ARTICLE

Predictors of mortality and endoscopic intervention in patients with upper gastrointestinal bleeding in the intensive care unit

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Abstract

Background: The outcomes of patients undergoing esophagogastroduodenoscopy (EGD) in the intensive care unit (ICU) for upper gastrointestinal bleeding (UGIB) are not well described. Our aims were to determine predictors of 30-day mortality and endoscopic intervention, and assess the utility of existing clinical-prediction tools for UGIB in this population.
Methods: Patients hospitalized in an ICU between 2008 and 2015 who underwent EGD were identified using a validated, machine-learning algorithm. Logistic regression was used to determine factors associated with 30-day mortality and endoscopic intervention. Area under receiver-operating characteristics (AUROC) analysis was used to evaluate established UGIB scoring systems in predicting mortality and endoscopic intervention in patients who presented to the hospital with UGIB.
Results: A total of 606 patients underwent EGD for UGIB while admitted to an ICU. The median age of the cohort was 62 years and 55.9% were male. Multivariate analysis revealed that predictors associated with 30-day mortality included American Society of Anesthesiologists (ASA) class (odds ratio [OR] 4.1, 95% confidence interval [CI] 2.2–7.9), Charlson score (OR 1.2, 95% CI 1.0–1.3), and duration from hospital admission to EGD (OR 1.04, 95% CI 1.01–1.07). Rockall, Glasgow-Blatchford, and AIMS65 scores were poorly predictive of endoscopic intervention (AUROC: 0.521, 0.514, and 0.540, respectively) and in-hospital mortality (AUROC: 0.510, 0.568, and 0.506, respectively).
Conclusions: Predictors associated with 30-day mortality include ASA classification, Charlson score, and duration in the hospital prior to EGD. Existing risk tools are poorly predictive of clinical outcomes, which highlights the need for a more accurate risk-stratification tool to predict the benefit of intervention within the ICU population.

Key words: upper gastrointestinal bleeding; esophagogastroduodenoscopy; intensive care unit

Introduction

Upper gastrointestinal bleeding (UGIB) is a common cause for hospital admission as well as intensive care unit (ICU) care. It is estimated to account for 300,000 admissions per year in the USA, with 23%–34% admitted to an ICU for further management [1, 2].

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Mortality from UGIB is estimated to be between 5% and 15%; mortality rates have remained stable in the last few decades despite advances in endoscopic tools and therapy, prevention of peptic-ulcer bleeding, and the use of high-dose proton pump inhibitor therapy [3]. Advances in the management of UGIB are presumed to be offset by a growing population of older patients with an increased number of co-morbidities. Patients admitted to the ICU often fall into this demographic. While endoscopy remains an overall safe procedure with rates of adverse events reported to be <1%, the risk becomes exponentially higher in patients with greater co-morbidities [4]. Therefore, while EGD remains a vital tool in the management of UGIB, it is one that should be used judiciously in a subset of critically ill patients.

The outcomes of patients undergoing EGD in the ICU for UGIB are not well elucidated and there are limited existing data regarding endoscopic findings, rate of intervention, and mortality within this population. Furthermore, clinical-prediction tools for UGIB such as the AIMS65, Glasgow-Blatchford, and Rockall scores have not been formally studied in a higher-risk population, specifically in patients who are admitted directly to the ICU with UGIB. Our aim was to characterize management of UGIB in an ICU population and determine clinical predictors of 30-day mortality and endoscopic intervention. We further examined whether existing risk scores for UGIB are predictive of endoscopic intervention and inpatient mortality in the ICU population.

Patients and methods

Study subjects

We performed a retrospective cohort study of adult patients who underwent an EGD for suspected UGIB while admitted to an ICU at the University of Chicago Medical Center—a large, urban tertiary care center, from January 2008 to September 2015. Patients were identified from an electronic data warehouse (EDW) using a validated machine-learning algorithm based on International Classification of Diseases, Ninth revision, Clinical Modification (ICD-9-CM) classification trees to identify patients with gastrointestinal bleeding. This algorithm was previously derived based on patients admitted to our medical center between 1 July 2001 and 30 June 2003, and validated based on a sample of patients admitted between 1 July 2003 and 30 June 2005 [5]. This data set included patients with unspecified gastrointestinal bleeding as their primary or secondary discharge diagnosis. Current procedural terminology (CPT) codes and billing encounters were then used to record the performance of an EGD and admission to an ICU (Supplementary Table 1) [6]. Manual chart review was performed to ensure the EGD was performed for the indication of suspected UGIB and occurred while the patient was admitted to an ICU. Primary and secondary ICD-9-CM discharge codes were used to identify medical co-morbidities at time of presentation [7]. Mortality data, including date of death, were available for all patients and linked to the Social Security Death Index.

Variables and definitions

We obtained baseline demographic data at the time of EGD, as well as laboratory data and vital signs upon presentation with UGIB, time from date of hospital admission to EGD, need for blood transfusion, length of hospital stay, and length of ICU stay utilizing the EDW. Manual chart review was utilized to determine whether the patient presented to the emergency department with the complaint of UGIB or whether the patient developed bleeding while already hospitalized for another condition. This was used as a distinguishing characteristic in the statistical analysis. EGD reports were reviewed to document endoscopic findings and intervention. Endoscopic intervention was defined as the use of mechanical clips, thermal therapy, epinephrine injection, or band ligation. Recurrent bleeding was based on clinical documentation of bleeding after the initial EGD as described by the medical team in the discharge summary, significant hemoglobin drop with concomitant overt bleeding, or need for repeat EGD during the same admission for the indication listed as recurrent UGIB.

The Glasgow-Blatchford, AIMS65, and Rockall scores were calculated for each patient in our cohort. During analysis, patients already hospitalized for another condition were excluded, as these scores were validated for use in those presenting to the emergency department with UGIB. The Glasgow-Blatchford score is predictive of medical or endoscopic intervention, while the AIMS65 and Rockall scores are predictive of in-hospital mortality. For summary of the scoring systems for each clinical-prediction tool, refer to Supplementary Tables 2–4 [8–10].

Outcomes

Our primary outcome of interest was predictors of 30-day mortality. Our secondary outcome of interest was predictors of endoscopic intervention. We also sought to evaluate the ability of existing UGIB risk scores (Rockall, Glasgow-Blatchford, and AIMS65) to accurately predict endoscopic intervention and in-hospital mortality in patients presenting with an UGIB directly admitted to the ICU.

Ethical consideration

The study was approved by the University of Chicago Institutional Review Board (IRB #16–00649) on 16 November 2016. The need for individual patient consent was waived by the Institutional Review Board as the study was performed in a retrospective manner.

Statistical analysis

Categorical variables were reported as percentages and continuous variables are reported as means with standard deviation (SD) and medians with the interquartile range (IQR) where specified. comparisons between categorical variables were made using the Fisher's exact test while Student's *t*-test and the Wilcoxon signed-rank test were used to analyse continuous variables. A two-sided *P*-value ≤ 0.05 was considered statistically significant. Univariate logistic regression was used to determine the relationship between clinical variables and the primary and secondary outcomes of interest. For the primary outcome of interest, variables significant in univariate analysis were included in a multivariate logistic-regression model to predict mortality.

For each of the calculated risk scores (Rockall, Glasgow-Blatchford, and AIMS 65), area under the receiver-operating characteristic (AUROC) curves were constructed to assess the relationship between each score and the occurrence of endoscopic intervention and in-hospital mortality only in those patients who presented with gastrointestinal bleeding as their primary reason for admission. Statistical analysis was conducted using JMP® 13.1.0 (SAS Institute, Inc., Cary, NC).

Results

Baseline characteristics

We identified 606 patients who underwent EGD for suspected UGIB while admitted to an ICU (Figure 1). The median age of the cohort was 62 years (IQR 54–71 years) and 55.9% ($n = 339$) were male. One hundred and eighty-eight patients (31.0%) developed bleeding while already hospitalized for another condition. The mean Charlson score was 3.95 (SD 2.77), with congestive heart failure ($n = 224$, 36.9%) and coronary artery disease ($n = 208$, 34.3%) as the most common co-morbidities. Of the 606 patients, 544 (89.8%) received a blood transfusion, 99 (16.3%) underwent endoscopic intervention, 86 (14.2%) developed recurrent bleeding, and 32 (5.2%) died from all causes within 30 days of undergoing EGD. The median time to death was 10.5 days (IQR 5.0–16.8). The majority (90.6%) of deaths were attributable to causes other than UGIB. The most common cause of death was cardiopulmonary disease ($n = 15$, 46.8%), followed by malignancy ($n = 5$, 15.6%) and liver failure ($n = 4$, 12.5%). Three patients (9.3%) died of UGIB. Additional information regarding the baseline cohort is presented in Table 1.

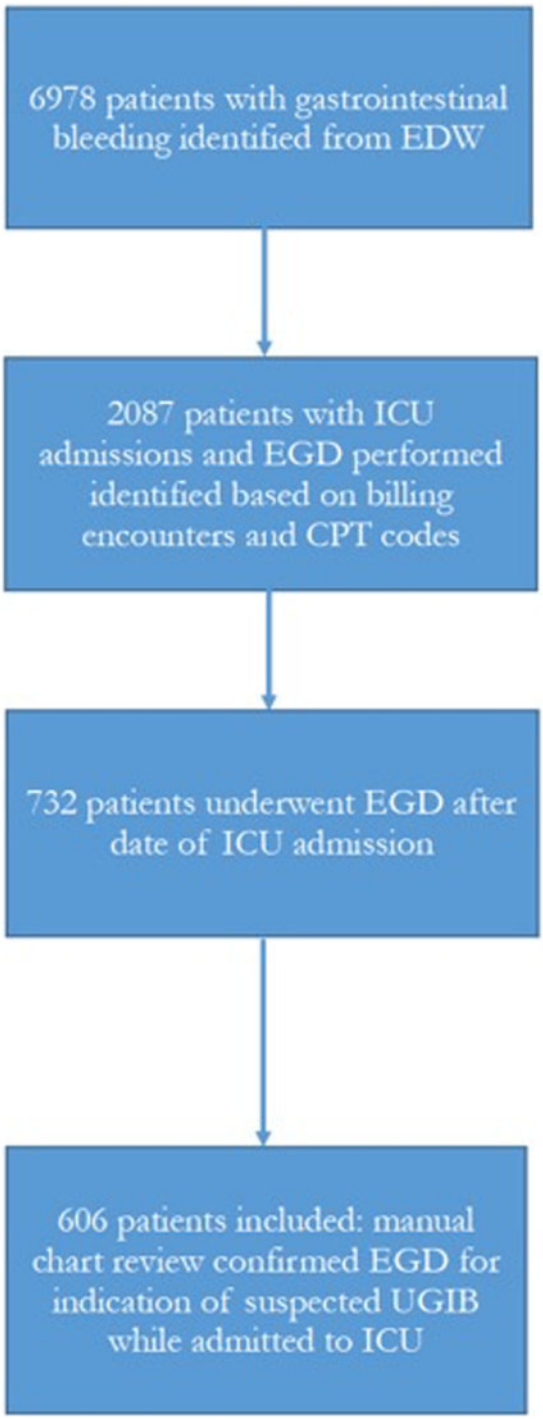

Figure 1. Flowchart of patient inclusion. EDW, Electronic Data Warehouse; ICU, intensive care unit; EGD, esophagogastroduodenoscopy; CPT, current procedural terminology.

Based on the American Society of Anesthesiologists (ASA) physical classification system [11], 518 patients (85.4%) were considered to be an ASA class of III or greater. Presenting clinical signs or patient symptoms prompting further evaluation with EGD is illustrated in Figure 2, with occurrence of melena as the most common patient presentation ($n = 251$, 41.4%). Of the 251 patients undergoing EGD for melena, 200 (79.7%) had a detectable source of bleeding. Rate of endoscopic intervention stratified by endoscopic finding is summarized in Figure 3. One hundred and fifty-two patients (25.1%) had high-risk endoscopic stigmata, classified as adherent clot, visible vessel, or an actively oozing or streaming lesion. Of the endoscopic findings, gastric ulcers most frequently underwent intervention (35.1%, 26/74).

Predictors of 30-day mortality

Patients who died within 30 days ($n = 32$) had longer duration in the ICU prior to EGD, longer duration from hospital admission to EGD, higher Charlson score, higher ASA class, and lower serum albumin (Table 1). Patients who developed UGIB while already hospitalized for another condition had greater all-cause 30-day mortality. Co-morbidities associated with mortality included a history of cerebrovascular accident. The performance of an endoscopic intervention (odds ratio [OR] 0.72, 95% confidence interval [CI] 0.25–2.10, $P = 0.548$) and the occurrence of recurrent bleeding (OR 1.09, 95% CI 0.41–2.90, $P = 0.869$) were not associated with 30-day mortality (Table 2). When included in a multivariate model, predictors associated with 30-day mortality included: ASA class (OR 4.14, 95% CI 2.18–7.87, $P < 0.001$), Charlson score (OR 1.19, 95% CI 1.02–1.34, $P = 0.014$), and duration from hospital admission to EGD (OR 1.04, 95% CI 1.01–1.07, $P = 0.026$) (Table 3).

Predictors of endoscopic intervention

Our secondary outcome of interest was to identify clinical predictors associated with endoscopic intervention. A higher Charlson score, high-risk endoscopic stigmata, presentation with hematemesis, and heart rate at presentation were associated with endoscopic intervention (Table 2). Importantly, duration of ICU admission prior to endoscopy was inversely associated with endoscopic intervention (OR 0.94, 95% CI 0.89–1.00, $P = 0.036$).

Risk score performance

For patients presenting to the emergency department with UGIB ($n = 418$), analysis showed that the Rockall, Glasgow-Blatchford, and AIMS65 scores were poorly predictive of in-hospital mortality (AUROC: 0.510, 0.568, and 0.506, respectively)

and endoscopic intervention (AUROC: 0.521, 0.514, and 0.540, respectively) (Supplementary Figures 1 and 2).

Discussion

UGIB is a common indication for admission to an ICU as well as a frequent complication that can develop while patients are already hospitalized for another condition. Although outcomes of patients with UGIB and the utility of clinical-prediction tools have been well described in the general population of those with UGIB, there are limited data on the outcomes of patients requiring EGD in the ICU setting. Previous studies about UGIB in the critically ill have primarily focused on the role of acid suppression in the prophylaxis and management of stress-related mucosal disease rather than identification of factors predictive of clinical outcomes in this population [12–14]. Herein, we sought to identify clinical predictors of all-cause 30-day mortality and endoscopic intervention in ICU patients who undergo endoscopic evaluation for UGIB. We determined that a higher ASA class, higher Charlson score, and longer duration from admission to EGD were predictors of 30-day mortality. Furthermore, established, validated tools to prognosticate UGIB were poorly predictive of intervention and in-hospital mortality in the ICU population.

Higher ASA class and Charlson score, both surrogate markers for a greater degree of systemic illness, were associated with overall 30-day mortality. Health-status scores have been found to be predictive of mortality in patients with UGIB in prior studies as well [15]. Inpatient status was also predictive of mortality on univariate analysis (OR 2.34, CI 1.14–4.78), consistently with previous studies that have demonstrated a 3-fold increase in mortality in patients who develop bleeding while hospitalized for another condition [15, 16].

Previous studies have demonstrated increased rates of endoscopic intervention and decreased length of stay with earlier endoscopy [17]. Some studies suggest that performance of endoscopy within 24 hours of presentation can favorably affect mortality rates in a subset of high-risk patients, while others do not demonstrate any effect on 30-day mortality [18, 19]. Although time from presentation to endoscopy was not clearly measured in our study, we were able to demonstrate that duration in the hospital was predictive of overall mortality. Second, as the majority of our population (68.9%) presented to the hospital with UGIB requiring ICU admission, we found an inverse association between duration of ICU admission and intervention. Higher-acuity patients admitted to the ICU with UGIB often have hemodynamic changes suggestive of active bleeding, and therefore have endoscopy performed sooner and more commonly require intervention. Previous studies have also shown early endoscopy to be associated

Table 1. Baseline characteristics stratified by 30-day mortality

Variable	Death ($n = 32$)	Alive ($n = 574$)	P-value
Age, years	63 (53–72)	62 (54–71)	0.94
Male sex	13 (40.6)	326 (56.8)	0.099
Time in ICU, days	4.62 ± 8.42	3.13 ± 7.38	0.049
Time to scope, days	9.25 ± 11.20	4.23 ± 7.96	0.003
ASA classification	3.50 ± 0.62	2.98 ± 0.57	<0.001
Anticoagulation use	4 (12.5)	159 (27.7)	0.066
Inpatient bleeding	16 (50.0)	172 (30.0)	0.029
Charlson score	5.34 ± 3.30	3.87 ± 2.72	0.015
Co-morbidities			
Coronary artery disease	12 (37.5)	196 (34.1)	0.704
Diabetes mellitus	10 (31.2)	146 (25.4)	0.532
History of cerebrovascular accident	4 (12.5)	22 (3.8)	0.042
Congestive heart failure	14 (43.8)	210 (36.6)	0.453
Pulmonary disease	11 (34.4)	172 (30.0)	0.693
Liver disease	9 (28.1)	107 (18.6)	0.244
End-stage renal disease	5 (15.6)	86 (15.0)	0.804
Cancer	8 (25.0)	99 (17.2)	0.242
Metastatic cancer	3 (9.4)	48 (8.4)	0.745
Labs on presentation			
Hemoglobin, g/dL	8.63 ± 2.16	8.94 ± 2.2	0.419
International normalized ratio	2.02 ± 1.59	1.96 ± 2.08	0.176
Blood urea nitrogen, mg/dL	45.38 ± 31.69	38.77 ± 29.53	0.224
Albumin, g/dL	2.84 ± 0.49	3.17 ± 0.69	0.004
Outcomes			
Recurrent bleeding	5 (15.6)	81 (14.6)	0.799
Blood transfusion	32 (100)	512 (89.2)	0.064
Endoscopic intervention	4 (12.5)	95 (16.6)	0.805

Values were presented as mean ± standard deviation, median (interquartile range), or *n* (%).
ICU, intensive care unit; ASA, American Society of Anesthesiologists.

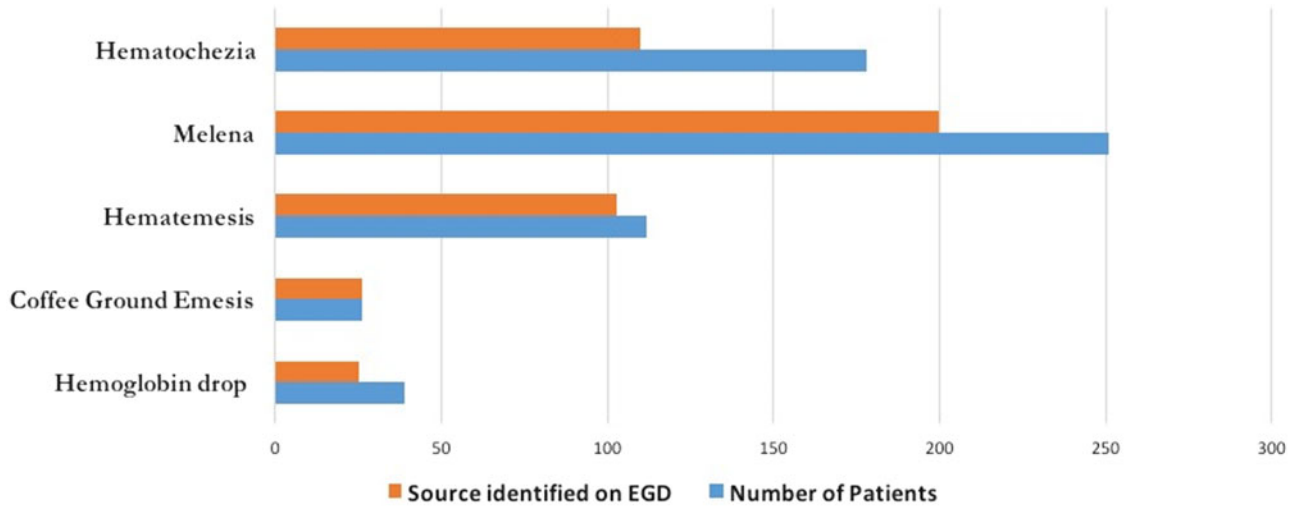

Figure 2. Indication for esophagogastroduodenoscopy (EGD)

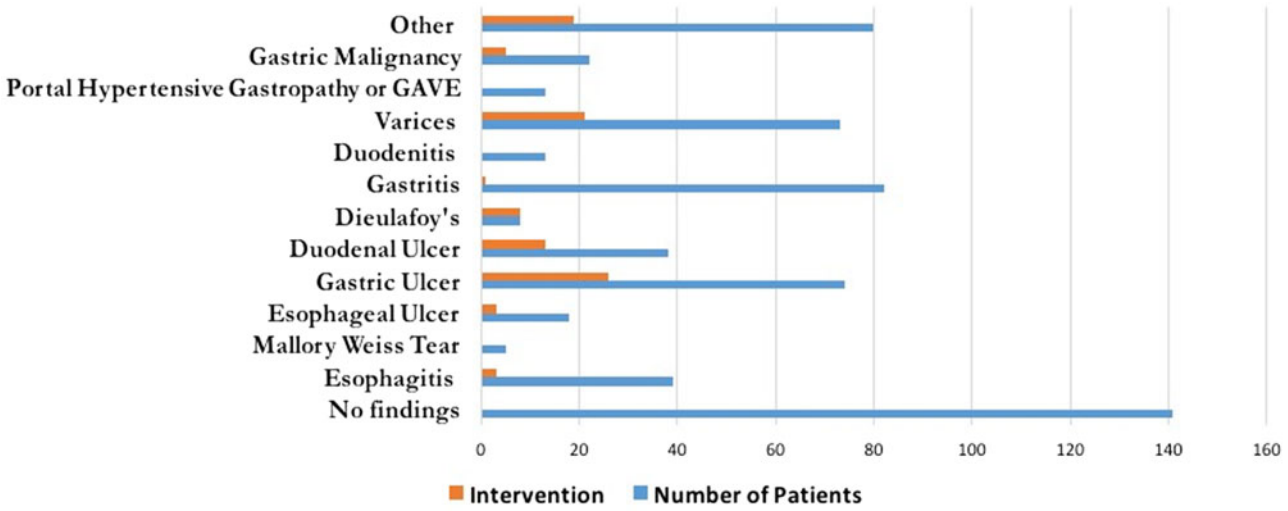

Figure 3. Endoscopic findings. GAVE, gastric antral vascular ectasia.

Table 2. Univariate analysis: predictors of mortality and endoscopic intervention

Variable	30-Day mortality		Endoscopic intervention	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age (years)	1.00 (0.98–1.03)	0.906	0.99 (0.98–1.01)	0.365
Gender (male/female)	0.52 (0.25–1.07)	0.077	1.26 (0.81–1.95)	0.307
Time in ICU (days)	1.02 (0.98–1.06)	0.275	0.94 (0.89–1.00)	0.036
Time from admission to scope (days)	1.04 (1.02–1.07)	0.002	0.98 (0.95–1.01)	0.201
Inpatient bleeding (yes/no)	2.34 (1.14–4.78)	0.022	0.91 (0.57–1.45)	0.684
Charlson score	1.18 (1.06–1.33)	0.004	1.08 (1.00–1.17)	0.039
ASA classification	4.50 (2.42–8.35)	<0.001	1.11 (0.77–1.60)	0.593
Anticoagulation use (yes/no)	0.37 (0.13–1.08)	0.069	0.69 (0.41–1.16)	0.165
Coronary artery disease (yes/no)	1.16 (0.55–2.42)	0.698	0.76 (0.47–1.21)	0.25
Cerebrovascular accident (yes/no)	3.58 (1.16–11.11)	0.023	0.66 (0.19–2.23)	0.502
Congestive heart failure (yes/no)	1.35 (0.66–2.77)	0.415	0.87 (0.56–1.37)	0.555
Hematemesis (yes/no)	0.81 (0.30–2.15)	0.669	2.71 (1.67–4.39)	<0.001
Melena (yes/no)	0.97 (0.47–1.99)	0.925	1.05 (0.68–1.62)	0.824
Heart rate (beats/minute)	1.00 (0.98–1.02)	0.860	1.01 (1.00–1.02)	0.039
Systolic blood pressure (mm Hg)	1.00 (0.98–1.01)	0.703	1.00 (0.99–1.00)	0.289
Hemoglobin (g/dL)	0.94 (0.80–1.10)	0.441	1.09 (0.99–1.20)	0.086
International normalized ratio	1.01 (0.86–1.19)	0.862	0.95 (0.83–1.08)	0.42
Blood urea nitrogen (mg/dL)	1.01 (1.00–1.02)	0.222	1.00 (0.99–1.00)	0.5
Albumin (g/dL)	0.49 (0.28–0.83)	0.009	0.84 (0.62–1.16)	0.292
High-risk endoscopic stigmata (yes/no)	0.83 (0.35–1.96)	0.668	36.15 (19.73–66.26)	<0.001
Endoscopic intervention (yes/no)	0.72 (0.25–2.10)	0.548	–	–
Recurrent bleeding (yes/no)	1.09 (0.41–2.90)	0.869	1.32 (0.74–2.36)	0.351

OR, odds ratio; CI, confidence interval; ICU, intensive care unit; ASA, American Society of Anesthesiologists.

Table 3. Multivariate analysis: predictors of 30-day mortality

Variable	Odds ratio (95% confidence interval)	*P*-value
Time to scope (days)	1.04 (1.01–1.07)	0.026
Charlson Score	1.19 (1.04–1.34)	0.014
ASA classification	4.14 (2.18–7.87)	<0.001

with increased use of endoscopic therapy [17]. Conversely, those patients who are admitted to the ICU for another cause and develop bleeding frequently have stress-related mucosal disease, which does not typically warrant intervention [2]. Clinical factors of severe UGIB such as presentation with hematemesis and initial heart rate were also associated with intervention, suggesting appropriate triage of patients to an ICU setting [20].

Performance of an endoscopic intervention and the occurrence of recurrent bleeding were not associated with 30-day mortality, reflective of the fact that the majority (90.6%) of the cohort died from causes other than UGIB. While endoscopy is generally considered a low-risk invasive procedure, the risk becomes exponentially higher in an ICU population. For patients who are considered an ASA class III, the OR of developing an adverse event associated with endoscopy is 3.90. For those with an ASA class of IV/V, the OR increases to 12.02 [21]. The majority (85.4%) of the patients in our study were classified

as an ASA class III or greater. The fact that our study revealed that a higher ASA class was predictive of mortality and endoscopic intervention does not affect mortality in a population largely classified as having severe systemic illness suggests that the risk–benefit ratio of endoscopy should be closely examined in this subset of patients.

Existing risk scores for UGIB, including the Glasgow-Blatchford, AIMS65, and Rockall scores, were calculated for each patient in our cohort. During analysis, patients already hospitalized for another condition were excluded. For reference, in the original validation group for the Glasgow-Blatchford Score, scores $\geq$6 were associated with a >50% risk of needing a medical or endoscopic intervention [9]. In-hospital mortality risk is considered high in patients with a complete Rockall score of >8 and in patients with two or more of the components of AIMS65 score [8, 10]. In those patients who presented to the emergency department with an UGIB and were subsequently admitted to the ICU, we did not find that any of the three scoring tools were predictive of endoscopic intervention or in-hospital mortality, which are the primary outcomes for which the scores are validated [8–10]. This may be an indication that the clinical features associated with in-hospital mortality or intervention specifically within the ICU population may not be represented in the existing risk scores. Previous studies have suggested the clinical factors associated with UGIB in critically ill patients include history of surgery, burns, major trauma, and respiratory failure requiring ventilation, which are not included as factors in the current prognostic scoring systems [22–24].

A risk-stratification score is needed within this population that is sicker and therefore at higher risk for adverse events from endoscopy. The development of an accurate scoring system for this high-risk population will better guide clinicians in decision-making on whether or not to pursue endoscopic evaluation. Determining clinical variables that will facilitate the identification of patients with UGIB in the ICU with a poor prognosis who may not benefit from endoscopic evaluation is of paramount importance. However, the heterogeneity of the ICU population does present a unique challenge to creating such a risk score. Future prospective studies could consider the utility of ICU scoring indices such as the APACHE score in prediction of mortality in this subset of patients presenting with primary UGIB admitted to the ICU.

Our data must be interpreted within the limitations of retrospective study design. Further adequately powered prospective studies are needed to elucidate clinical predictors of mortality and endoscopic intervention. The initial patient cohort was identified based on an ICD-9-CM code for unspecified gastrointestinal bleeding and lower gastrointestinal bleeding. Although a validated algorithm for identification of patients with exclusive UGIB was not used for this study, manual chart review was utilized to ensure accuracy of inclusion of patients who underwent EGD for suspected UGIB while admitted to an ICU. The effects on time to endoscopy on mortality in this population should be further clarified. Given the limitations of our data set, we were not able to gather specifics about time of presentation from bleeding or ICU admission to endoscopy as quantified in hours; therefore, time was reported in days. This clarification would provide valuable information regarding the role of timing from bleeding presentation to endoscopy in clinical outcomes within the critically ill. Finally, the existing risk-stratification tools for UGIB should be calculated for ICU patients in a prospective manner that may more accurately determine their utility within this population.

In conclusion, predictors associated with 30-day mortality include ASA classification, Charlson score, and duration from admission to endoscopy. Endoscopic intervention was not associated with 30-day mortality. Existing risk tools were not found to be predictive of clinical outcomes, which highlights the need for a more accurate risk-stratification tool to predict the benefit of intervention within the ICU population.

Supplementary data

Supplementary data is available at *Gastroenterology Report* online.

Authors' contributions

V.L.R. contributed to conception and design, acquisition, analysis or interpretation, drafting of the manuscript. N.G., E.S., and T.W. contributed to acquisition, analysis or interpretation, critical review of the manuscript. A.A., K.G.R., and N.S. contributed to conception and design, analysis or interpretation, critical review of the manuscript. All authors read and approved the final manuscript.

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Conflicts of interest

None declared.

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