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The Time of Endoscopy for Nonvariceal Upper Gastrointestinal Bleeding: An Observational Study

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Objectives: In cases of nonvariceal upper gastrointestinal bleeding (NVUGIB), endoscopic intervention within the first 24 hours is widely recommended. However, data on the efficacy of urgent endoscopy are limited. Here, we used the Glasgow–Blatchford score to assess bleeding outcomes based on time-to-endoscopy. **Methods:** Prospectively collected multicenter data, which included 1554 patients with NVUGIB, were retrospectively reviewed between February 2011 and December 2013. Based on time-to-endoscopy, patients were grouped into the early (<24 hours) versus the delayed (≥24 hours) group and the urgent (<6 hours) versus the non-urgent (≥6 hours) group. The rates of re-bleeding, mortality, secondary intervention, transfusion, and morbidity aggravation were analyzed. **Results:** The mean time-to-endoscopy and median Glasgow–Blatchford score were 33.0±75.5 hours and 12 (range: 1–23), respectively. Univariate analyses revealed that in the delayed endoscopy group, the transfusion and re-bleeding rates were higher (hazard ratio [HR]: 1.257, 95% confidence interval [CI]: 1.026–1.540) and lower (HR: 0.610, 95% CI: 0.413–0.901), respectively. Multivariate analysis revealed that delayed endoscopy was a significant factor for lower re-bleeding rate (HR: 0.576, 95% CI: 0.387–0.859), which was prominent in the low-risk group (HR: 0.417, 95% CI: 0.225–0.774). Multivariate analysis showed that when compared with the low-risk group, in-hospital comorbidity aggravation was more common in high-risk patients who underwent non-urgent endoscopy (HR: 2.957, 95% CI: 1.045–6.454). **Conclusions:** In low-risk patients, delayed endoscopy is sufficient for NVUGIB management. In high-risk patients, urgent endoscopy reduced comorbidity aggravation during hospital care.

Keywords Bleeding; Endoscopy; Mortality; Morbidity.

INTRODUCTION

The diagnosis and management of acute nonvariceal upper gastrointestinal bleeding (NVUGIB) is based on upper gastrointestinal (GI) endoscopy.[1,2] However, the appropriate timing of endoscopy in NVUGIB cases is controversial, although endoscopic intervention within the first 24 hours (early endoscopy) is widely recommended.[1-5] A systematic review[6] showed that in low-risk patients, early endoscopy led to prompt triaging and treatment, and reduced hospital stay. However, in high-risk patients, when compared with delayed endoscopy, early endoscopy did not decrease mortality rates, except in cases with

re-bleeding or those requiring transfusion or surgery.

For improved clinical outcomes, triage is necessary to group patients as low- or high-risk. The Glasgow–Blatchford bleeding score (GBS) and the admission Rockall score are pre-endoscopic prognostic indices. Because of its simple clinical laboratory variables and ability to predict the need for treatment, the GBS is preferable to the admission Rockall score.[7] Moreover, two studies[8,9] showed that in predicting the need for endoscopic therapy, surgery, and transfusion, the GBS was superior to the admission Rockall score and similar to the full Rockall score. GBS was equally capable of predicting both Rockall scores.

In several randomized controlled trials and retrospective cohort studies, the definition of urgent endoscopy ranges from 2–12 hours.[2,10-12] Although several studies[10,12] have reported that urgent endoscopy did not improve clinical outcomes, such as re-bleeding, the need for surgery, and the duration of hospital stay, a randomized study[13] and an observational study[14] found that in high-risk patients, urgent endoscopy reduced the need for transfusion and hospitalization, and predicted hospital mortality (GBS: ≥12). However, because of limited data, the effect of early endoscopy, especially urgent endoscopy, in selected subgroups after risk stratification is not well established. Thus, using GBS, this study evaluated bleeding outcomes based on time-to-endoscopy.

METHODS

Study design and patients

Data were collected after informed consent from eight teaching hospitals at which 24-hour endoscopy services were offered by an emergency endoscopy team made up of an expert endoscopist, a trainee endoscopist, and a trained nurse. The following data were entered into the bleeding registry protocol: 1) demographic data (age and sex), 2) ulcer history, 3) medication history (nonsteroidal anti-inflammatory drugs, steroids, antiplatelet drugs, anticoagulants, and proton pump inhibitors [PPIs]), 4) social history (alcohol use and smoking), 5) vital signs (blood pressure, heart rate, respiratory rate, and body temperature), 6) laboratory variables (hemoglobin [Hb], platelet count, blood urea nitrogen level, and prothrombin time), 7) comorbidities (ischemic heart disease, heart failure, hypertension, hepatic disease, renal failure, cerebrovascular disease, peripheral vascular disease, diabetes, metastatic cancer, hematological cancer, and surgical history), 8) endoscopic findings, 9) endoscopic therapeutic modality (epinephrine injection, hemoclipping, electrocoagulation, argon plasma coagulation, and band ligation), 10) clinical outcome (re-bleeding, transfusion, secondary intervention, in-hospital comorbidity aggravation, and 30-day mortality), 11) pre-endoscopic prognostic score (GBS), and 12) time-to-endoscopy.

Data from 1984 adult patients, who presented with acute upper GI bleeding, were collected prospectively. Of these, 366 patients with gastroesophageal varices or portal hypertensive gastropathy, six with oral bleeding, lower GI bleeding, or bleeding caused by a foreign body, and 58 with incomplete data were excluded. Finally, the study involved 1554 patients who had undergone endoscopy for NVUGIB between February 2011 and December 2013. This study was approved by Institutional Review Board in Kyungpook National University Chilgok Hospital (KNUMC_11-1011) and registered with the Clinical Research Information Service (https://cris.nih.go.kr; accession number KCT0000514).

Interventions and definitions

NVUGIB was defined as the presence of hematemesis, coffee-ground vomitus, melena, and hematochezia confirmed using upper endoscopy and/or colonoscopy. General management including PPI administration was performed in the emergency room according to the international consensus recommendations on the management of patients with NVUGIB. These include high-dose intravenous PPI therapy (e.g., pantoprazole 80 mg bolus followed by 8 mg/h continuous infusion for 3days).[3,5] Time-to-endoscopy was defined as the time between initial presentation with upper GI bleeding and index endoscopy symptoms. Because this study lacked a randomized controlled design, optimal endoscopy timing, endoscopic treatment, transfusion, and secondary interventions were decided by the on-call gastroenterology consultant or the endoscopist. In this study, drugs that enhance visibility by facilitating gastric emptying, such as erythromycin, were not used.

Based on the time-to-endoscopy, patients were grouped into the early (<24 hours) versus delayed endoscopy (≥24 hours) group and the urgent (<6 hours) versus the non-urgent endoscopy group (≥6 hours). Tachycardia (heart rate: ≥100 beats/minute) and/or hypotension (systolic blood pressure: <100 mmHg) indicated shock.[15] Re-bleeding was indicated by the following: 1) hematemesis after six hours following index endoscopy, 2) melena or hematochezia after stool color normalization, 3) uncontrolled tachycardia or hypotension during persistent melena or hematochezia, within eight hours after index endoscopy, 4) a Hb decrease of >2 g/dL during persistent melena or hematochezia, and 5) tachycardia or hypotension after vital sign normalization for more than an hour. Mortality was classified based on the cause of death (bleeding or all-cause). Data on clinical outcomes, including in-hospital morbidity and mortality, re-bleeding, transfusion, secondary interventions, hospital stay, and Hb level changes were record-

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ed. Thirty-day mortality data were obtained four weeks after discharge from patient data at the outpatient department. For some patients, follow-up was conducted by phone. Comorbidity data were classified based on a modified version of the Charlson Comorbidity Index, and diseases were selected based on their association with mortality.[16] Using clinical and laboratory approaches, the attending physician prospectively evaluated pre-existing comorbidity aggravation. Secondary interventions were performed through surgery and/or angiography. During endoscopy, active bleeding was described as spurting or oozing. Patients with a GBS of >12 were classified as high-risk.

Statistical methods

Data were analyzed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA). Univariate analysis was used to compare factors that can affect clinical outcomes (demographics, laboratory variables, and clinical variables) based on time-to-endoscopy. Numerical and categorical data were compared using a Student t-test and chi-square test, respectively. Numerical data are presented as mean±standard deviation or median and interquartile range. Univariate (chi-square test) and multivariate (logistic regression) analyses were used to investigate clinical outcomes based on time-to-endoscopy. A chi-square test was used to compare unadjusted clinical outcome differences. Multivariate analysis allowed adjustment for confounding factors that have the potential to predict clinical outcomes. The odds ratios (OR) and 95% confidence intervals (CI) of various laboratory and clinical factors associated with clinical outcomes were calculated through logistic regression analysis using a backward method. All p-values were two-tailed, and $p<0.05$ was considered statistically significant. For subgroup analysis, based on GBS, pre-endoscopic risk was classified as high or low.

RESULTS

Patient characteristics

The patients' mean time-to-endoscopy, mean age, and median GBS were 33.0±75.5 hours, 63.0±16.3 years, and 12 (range: 1–23), respectively. Table 1 shows a summary of the baseline characteristics based on time-to-endoscopy (early versus delayed and urgent versus non-urgent). The frequencies of early and delayed endoscopy were approximately equal (n=785 and n=769, respectively). In the early and delayed endoscopy groups, demographics (age and sex) as well as laboratory and clinical variables, were similar. However, patients who underwent early endoscopy had lower blood urea nitrogen (>20 mg/dL, 69.1% versus 79.0%) and a higher initial Hb level (9.6±3.0 g/dL versus 8.8±2.8 g/dL). Patients who underwent delayed endoscopy were more likely to have an ulcer history. Hospital stay was significantly shorter in the early endoscopy group.

When compared with non-urgent endoscopy, urgent endoscopy was performed less frequently (n=1227 versus n=327, respectively). Patients who underwent urgent endoscopy had favorable laboratory variables, except blood urea nitrogen, which was elevated. Of the clinical variables, GBS, ulcer history, therapeutic endoscopy, and hepatic disease history were significantly different. The patients who underwent urgent endoscopy were less likely to have an ulcer history (14.6% versus 20.6%) or hepatic disease (7.6% versus 11.5%). GBS values of >12 were more common in the urgent endoscopy group (49.2% versus 37.0%). However, during endoscopy, the frequencies of active bleeding were similar in the urgent and non-urgent groups (19.2% versus 16.2%, respectively), although therapeutic endoscopy procedures were more common in the non-urgent endoscopy group than in the urgent group (60.4% versus 48.9%). When compared with the non-urgent endoscopy group, hospital stay was significantly shorter in the urgent endoscopy group.

Early versus delayed endoscopy

Table 2 shows a summary of clinical outcomes (overall mortality, bleeding-associated mortality, re-bleeding, comorbidity aggravation, secondary interventions, and the need for transfusion), classified by early and delayed endoscopy. Univariate analysis revealed that the transfusion and re-bleeding rates were higher and lower in the delayed endoscopy group (OR: 1.257, 95% CI: 1.026–1.540, p=0.027 and OR: 0.610, 95% CI: 0.413–0.901, p=0.012, respectively). However, mortality, comorbidity aggravation, and the required secondary intervention were not significantly different. Multivariate analysis revealed that early endoscopy was a significant factor for re-bleeding, which, based on univariate analysis, was less frequent in the delayed endoscopy group (OR: 0.576, 95% CI: 0.387–0.859, p=0.007).

Urgent versus non-urgent endoscopy

Comorbidity aggravation was lower in the urgent endoscopy group, based on univariate (OR: 2.234, 95% CI: 1.061–4.705, p=0.030) and multivariate (OR: 2.195, 95% CI: 1.033–4.665, p=0.041) analyses (Table 3). However, unlike in the early and delayed endoscopy groups, re-bleeding and transfusion rates were not significant outcomes. As in the early endoscopy group, urgent endoscopy was not a significant factor for mortality and secondary intervention.

Subgroup analysis of the low- and high-risk groups

Multivariate analysis revealed that in the low-risk group, clinical outcomes, except re-bleeding, were not significantly different in the early versus delayed endoscopy groups (Table 4).

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Table 1. Patient characteristics according to time to endoscopy and GBS

Characteristics	Time to endoscopy <24 hours (n=785)	Time to endoscopy ≥24 hours (n=769)	*p*-value	Time to endoscopy <6 hours (n=327)	Time to endoscopy ≥6 hours (n=1227)	*p*-value	GBS ≤12 (n=938)	GBS >12 (n=616)	*p*-value
Age (yr)	63.6±16.7	62.4±15.9	0.164	64.7±15.6	62.6±16.5	0.034	60.1±17.1	67.5±14.0	<0.001
Male	73.6	70.2	0.944	74.0	70.2	0.578	75.9	70.2	0.014
Prothrombin time (≥14 seconds)	26.3	23.7	0.242	20.4	26.3	0.031	19.4	33.7	0.821
Platelet count (≤150×10^3/mm^3)	16.1	18.4	0.233	13.1	18.4	0.025	13.8	22.5	<0.001
Blood urea nitrogen (>20 mg/dL)	69.1	79.0	<0.001	79.0	77.5	<0.001	63.5	90.9	<0.001
Hemoglobin (g/dL)	9.6±3.0	8.8±2.8	<0.001	9.6±3.1	9.1±2.9	0.008	10.1±3.0	7.7±2.1	<0.001
Systolic blood pressure (mmHg)	116.5±25.5	117.2±23.4	0.534	117.7±26.5	116.6±23.9	0.479	121.3±22.2	110.1±26.3	<0.001
Heart rate (bpm)	91.2±19.2	89.1±19.4	0.237	90.4±19.5	90.6±19.3	0.888	89.5±19.0	92.0±19.7	0.013
Shock	10.5	9.3	0.426	10.7	9.7	0.620	4.1	18.8	<0.001
Glasgow-Blatchford score >12	39.7	39.5	0.931	49.2	37.0	<0.001	0	100	<0.001
Cancer bleeding*	2.5	3.2	0.409	3.6	2.6	0.348	50.5	50.7	0.931
Previous medication with bleeding risk†	34.5	33.9	0.809	33.9	34.3	0.901	2.3	3.7	0.110
Previous ulcer history	17.0	21.7	0.020	14.6	20.6	0.016	29.2	41.8	<0.001
Duration of hospital stay (days)	9.3±10.2	19.7±75.0	<0.001	9.3±9.5	15.8±59.9	0.049	11.2±38.9	19.3±69.9	0.003
Comorbidity	65.7	64.2	0.537	64.5	65.1	0.842	20.8	17.0	0.060
Hepatic disease	10.3	11.1	0.582	7.6	11.5	0.044	57.3	76.6	<0.001
Renal disease	5.8	4.6	0.299	6.7	4.8	0.187	9.2	12.9	0.021
Malignant disease	5.3	4.5	0.468	7.0	4.4	0.051	3.8	6.6	0.012
Therapeutic endoscopy (intervention)	58.1	60.7	0.947	48.9	60.4	<0.001	7.0	4.4	0.051
Active bleeding on endoscopy	16.9	16.7	0.930	19.2	16.2	0.191	56.2	60.7	0.084
Presentation-to-endoscopy time (<24 hr)	-	-	-	-	-	-	50.5	50.7	0.931
Presentation-to-endoscopy time (<6 hr)	-	-	-	-	-	-	17.6	26.1	<0.001

Data are presented as mean±standard deviation or percentage.
*Bleeding caused by primary or metastatic upper gastrointestinal malignancy; †Antiplatelet drugs (NSAIDs, aspirin, clopidogrel, cilostazol, etc.), anticoagulants (heparin, low molecular weight heparin, warfarin), new anticoagulants (dabigatran, rivaroxaban, etc.) and steroid.
GBS, Glasgow–Blatchford bleeding score; bpm, beats per minute; NSAIDs, nonsteroidal anti-inflammatory drugs.

Table 2. Univariate and multivariate analysis of clinical outcomes (early versus delayed endoscopy)

	Univariate				Multivariate		
	Early endoscopy† (n=785)	Delayed endoscopy‡ (n=769)	OR* (95% CI)	*p*-value	Time to endoscopy	OR* (95% CI)	*p*-value
Overall mortality	4.3	2.6	0.590 (0.336–1.034)	0.063	Early endoscopy (n=785)	-	0.116
					Delayed endoscopy (n=769)	0.621 (0.342–1.125)	
Mortality related to bleeding	1.6	1.4	0.862 (0.384–1.936)	0.718	Early endoscopy (n=785)	-	0.847
					Delayed endoscopy (n=769)	0.919 (0.391–2.163)	
Re-bleeding	9.0	5.7	0.610 (0.413–0.901)	0.012	Early endoscopy (n=785)	-	0.007
					Delayed endoscopy (n=769)	0.576 (0.387–0.859)	
Aggravation of comorbidity	4.5	4.8	1.055 (0.659–1.687)	0.825	Early endoscopy (n=785)	-	0.903
					Delayed endoscopy (n=769)	1.031 (0.628–1.695)	
Secondary intervention	2.2	1.6	0.733 (0.357–1.506)	0.396	Early endoscopy (n=785)	-	0.399
					Delayed endoscopy (n=769)	0.721 (0.337–1.541)	
Transfusion	57.1	62.6	1.257 (1.026–1.540)	0.027	Early endoscopy (n=785)	-	0.711
					Delayed endoscopy (n=769)	1.047 (0.823–1.331)	

Data are presented as percentage.
*Reference category <24 hours OR=1.0; †Early endoscopy <24 hours; ‡Delayed endoscopy ≥24 hours.
OR, odds ratio; CI, confidence interval.

Table 3. Univariate and multivariate analysis of clinical outcomes (urgent versus non-urgent endoscopy)

	Univariate				Multivariate		
	Urgent endoscopy* (n=327)	Non-urgent endoscopy† (n=1227)	OR‡ (95% CI)	*p*-value	Time to endoscopy	OR‡ (95% CI)	*p*-value
Overall mortality	4.2	3.2	0.753 (0.405–1.402)	0.370	Urgent endoscopy (n=327)	-	0.461
					Non-urgent endoscopy (n=1227)	1.282 (0.662–2.483)	
Mortality related to bleeding	2.4	1.3	0.527 (0.223–1.242)	0.137	Urgent endoscopy (n=327)	-	0.396
					Non-urgent endoscopy (n=1227)	0. 662 (0.256–1.725)	
Re-bleeding	7.0	7.4	1.071 (0.667–1.721)	0.776	Urgent endoscopy (n=327)	-	0.390
					Non-urgent endoscopy (n=1227)	1.247 (0.754–2.065)	
Aggravation of comorbidity	2.4	5.3	2.234 (1.061–4.705)	0.030	Urgent endoscopy (n=327)	-	0.041
					Non-urgent endoscopy (n=1227)	2.195 (1.033–4.665)	
Secondary intervention	1.2	2.2	1.817 (0.631–5.230)	0.261	Urgent endoscopy (n=327)	-	0.233
					Non-urgent endoscopy (n=1227)	0.509 (0.168–1.545)	
Transfusion	56.2	60.8	1.209 (0.945–1.548)	0.131	Urgent endoscopy (n=327)	-	0.641
					Non-urgent endoscopy (n=1227)	1.073 (0.798–1.444)	

Data are presented as percentage.
*Urgent endoscopy <6 hours; †Non-urgent endoscopy ≥6 hours; ‡Reference category urgent endoscopy OR=1.0.
OR, odds ratio; CI, confidence interval.

When compared with the early endoscopy group, the re-bleeding rate was significantly lower in the delayed endoscopy group (OR: 0.417, 95% CI: 0.225–0.774, *p*=0.006). However, multivariate analysis revealed that in patients with a GBS score of >12, early endoscopy was not superior to delayed endoscopy based on clinical outcomes. In low-risk patients, the urgent and non-urgent endoscopy groups did not differ significantly (Table 5). However, when compared with the low-risk group, urgent endoscopy was significantly less likely to affect comorbidity aggravation in the high-risk group (OR: 2.957, 95% CI: 1.045–6.454, *p*=0.040). In the low- and high-risk groups, early and urgent endoscopy did not affect mortality, the need for secondary intervention, and the transfusion rate favorably. In the high-risk group, re-bleeding was not influenced by time-to-endoscopy.

Table 4. Subgroup analysis of clinical outcomes by the risk group (early versus delayed endoscopy)

	Low risk group*			High risk group†		
	Time to endoscopy	OR‡ (95% CI)	*p*-value	Time to endoscopy	OR‡ (95% CI)	*p*-value
Overall mortality	Early endoscopy§ (n=473)	-	0.445	Early endoscopy (n=312)		0.116
	Delayed endoscopy‖ (n=465)	0.656 (0.222–1.934)		Delayed endoscopy (n=304)	0.553 (0.264–1.157)	
Mortality related to bleeding	Early endoscopy (n=473)	-	0.415	Early endoscopy (n=312)		0.409
	Delayed endoscopy (n=465)	2.335 (0.305–17.900)		Delayed endoscopy (n=304)	0.644 (0.227–1.831)	
Re-bleeding	Early endoscopy (n=473)	-	0.006	Early endoscopy (n=312)		0.251
	Delayed endoscopy (n=465)	0.417 (0.225–0.774)		Delayed endoscopy (n=304)	0.716 (0.405–1.266)	
Aggravation of comorbidity	Early endoscopy (n=473)	-	0.569	Early endoscopy (n=312)		0.576
	Delayed endoscopy (n=465)	1.274 (0.533–2.934)		Delayed endoscopy (n=304)	0.829 (0.429–1.600)	
Secondary intervention	Early endoscopy (n=473)	-	0.232	Early endoscopy (n=312)		0.983
	Delayed endoscopy (n=465)	0.494 (0.155–1.571)		Delayed endoscopy (n=304)	0.988 (0.326–2.992)	
Transfusion	Early endoscopy (n=473)	-	0.681	Early endoscopy (n=312)		0.189
	Delayed endoscopy (n=465)	1.067 (0.784–1.451)		Delayed endoscopy (n=304)	1.341 (0.865–2.078)	

*Glasgow-Blatchford score (GBS) ≤12, total 938 patients; †Glasgow-Blatchford score (GBS) >12, total 616 patients; ‡Reference category <24 hours OR=1.0; §Early endoscopy <24 hours; ‖Delayed endoscopy ≥24 hours.
OR, odds ratio; CI, confidence interval.

Table 5. Subgroup analysis of clinical outcomes by the risk group (urgent versus non-urgent endoscopy)

	Low risk group*			High risk group†		
	Time to endoscopy	OR‡ (95% CI)	*p*-value	Time to endoscopy	OR‡ (95% CI)	*p*-value
Overall mortality	Urgent endoscopy§ (n=166)	-	0.608	Urgent endoscopy (n=161)		0.235
	Non-urgent endoscopy‖ (n=772)	0.702 (0.182-2.711)		Non-urgent endoscopy (n=455)	1.640 (0.725-3.710)	
Mortality related to bleeding	Urgent endoscopy (n=166)	-	0.478	Urgent endoscopy (n=161)		0.203
	Non-urgent endoscopy (n=772)	0.393 (0.030-5.167)		Non-urgent endoscopy (n=455)	2.055 (0.677-6.237)	
Re-bleeding	Urgent endoscopy (n=166)	-	0.934	Urgent endoscopy (n=161)		0.237
	Non-urgent endoscopy (n=772)	1.032 (0.485-2.199)		Non-urgent endoscopy (n=455)	1.544 (0.752-3.170)	
Aggravation of comorbidity	Urgent endoscopy (n=166)	-	0.109	Urgent endoscopy (n=161)		0.040
	Non-urgent endoscopy (n=772)	0.293 (0.065-1.312)		Non-urgent endoscopy (n=455)	2.957 (1.045-6.454)	
Secondary intervention	Urgent endoscopy (n=166)	-	0.390	Urgent endoscopy (n=161)		0.399
	Non-urgent endoscopy (n=772)	0.490 (0.097-2.489)		Non-urgent endoscopy (n=455)	0.485 (0.090-2.611)	
Transfusion	Urgent endoscopy (n=166)	-	0.308	Urgent endoscopy (n=161)		0.681
	Non-urgent endoscopy (n=772)	0.811 (0.541-1.213)		Non-urgent endoscopy (n=455)	0.897 (0.535-1.506)	

*Glasgow-Blatchford score (GBS) ≤12, total 938 patients; †Glasgow-Blatchford score (GBS) >12, total 616 patients; ‡Reference category <6 hours OR=1.0; §Urgent endoscopy <6 hours; ‖Non-urgent endoscopy ≥6 hours.
OR, odds ratio; CI, confidence interval.

DISCUSSION

Here, we show that mortality was not associated with time-to-endoscopy in the high- and low-risk subgroups, which is consistent with previous findngs.[13,17-20] However, because of a simple risk stratification by clinical variables, such as age and vital signs, these studies did not have methodical criteria for each risk group. Therefore, we analyzed clinical outcomes, including mortality, using GBS, which is preferred over full and admission Rockall scores for the prediction of mortality and the need for intervention and transfusion.[8,9,21]

Our findings indicate that re-bleeding was associated with time-to-endoscopy in limiting conditions. When compared with the early endoscopy group, the re-bleeding rate was significantly lower in the delayed endoscopy group. However, it did not differ significantly in the urgent endoscopy versus the non-urgent endoscopy group. The GBS-based subgroup analysis results are particularly worth noting. Lower re-bleeding rates were observed in the low-risk patients who underwent delayed endoscopy than in those who underwent early endoscopy. However, based on time-to-endoscopy, re-bleeding rates did not differ in the low-risk patients who underwent urgent endoscopy when compared with those in the non-urgent endoscopy or high-risk groups. This study revealed that in patients who underwent endoscopy at 12–24 hours and >24 hours, re-bleeding rates were lower in patients in the non-therapeutic endoscopy group who underwent endoscopy within 12 hours. We believe that the differences in the results when compared with our study's results, are because of the effects of PPIs and visualization during endoscopy. Several randomized trials involving patients with bleeding ulcers have demonstrated the protective effects of PPIs in all patients with continued bleeding and surgery.[22-24] Although active bleeding rates did not differ between the delayed endoscopy and early endoscopy groups, we believe that regarding coagulation, patients who underwent delayed endoscopy had more time to benefit from PPIs. Because high-risk bleeding stigmata is a well-known risk factor for re-bleeding, the study[25] that showed that time-to-endoscopy improves a lesion from one that needs endoscopic hemostasis to a low-risk lesion that can be treated pharmacologically warrants attention. We think that the other reason is superior visualization than early endoscopy. Performing endoscopy during or soon after active bleeding is controlled obscures the bleeding site, making endoscopic hemostasis difficult.[25] We therefore speculate that regarding re-bleeding, patients who undergo delayed endoscopy, especially low-risk patients, benefit from sufficient PPI effects and superior visualization.

Our results on mortality and re-bleeding differ from previous studies. Some studies emphasize the role of early endoscopy in mortality reduction.[26] A Danish nationwide cohort study showed that in patients with hemodynamic instability, early endoscopy (6–24 hours after admission) was associated with lower in-hospital mortality when compared with endoscopy outside this time frame.[27] A retrospective study assessed a composite of inpatient deaths from any cause, inpatient re-bleeding, need for surgical or radiologic intervention, or endoscopic re-intervention in patients with NVUGIB and found that the risk of reaching the composite outcome increased by more than five-fold in patients who underwent urgent endoscopy (<12 hours), especially in low-risk patients. However, in high-risk patients, time-to-endoscopy was not a significant primary outcome predictor. Therefore, in low-risk patients, urgent endoscopy is a predictor of worse outcomes.[28] Although these two studies highlighted the role of urgent endoscopy, they were not consistent with our results. However, most recent studies on the role of urgent endoscopy reported negative results. A randomized study that compared 30-day mortality rates in high-risk patients who underwent urgent (within six hours) or early (in 6–24 hours) endoscopy found that mortality did not differ between the groups.[29] Moreover, two retrospective studies did not find convincing evidence on the role of urgent endoscopy in reducing endoscopic therapy, recurrent bleeding, and 30-day mortality.[20,30] A Hong Kong retrospective study reported that when compared with early endoscopy (6–24 hours) urgent endoscopy (<6 hours) had worse outcomes, with a higher 30-day all-cause mortality.[31] These observations are consistent with our finding that like early endoscopy, urgent endoscopy was not a significant factor for mortality and secondary intervention. Unexpectedly, we found that when compared with non-urgent endoscopy, urgent endoscopy was associated with in-hospital comorbidity aggravation. Specifically, we found that the comorbidity aggravation rate was lower in high-risk patients who underwent urgent endoscopy than in those who received non-urgent endoscopy. Although time-to-endoscopy did not affect the mortality rate in our study, several studies have reported that patients with peptic ulcer bleeding or upper GI bleeding have worse long-term mortality rates. We reasoned that although urgent endoscopy was not a significant mortality factor in this study, long-term mortality may rise over time, and that it might be affected by comorbidities. Therefore, in high-risk patients with high comorbidity levels and NVUGIB, urgent endoscopy may improve long-term mortality by decreasing comorbidity aggravation. However, long-term studies are needed to prove causal relationships.

Our findings are consistent with several recent guidelines suggesting that urgent endoscopy does not improve patient prognosis,[32] and that early endoscopy (within 24 hours) is sufficient.[33] Generally, previous guidelines recommend endosco-

py within 24 hours[5] or that very early endoscopy (in <12 hours) should be considered in patients with high-risk clinical features, like hemodynamic instability.[2] Although this is an earlier study than recent guidelines, its results reflect current clinical recommendations. However, the 2020 Korean NVUGIB guidelines remain conservative, and recommend endoscopy within 24 hours and that the need for urgent endoscopy should be decided by the physician.[34] The recommendations are based on a large 2018 study,[35] which enrolled patients with a GBS of >7 and compared outcomes like mortality and re-bleeding in the urgent (six hours) versus elective (6–48 hours) endoscopy groups. The mortality rate (1.6% versus 3.8%), but not re-bleeding, was significantly different. The authors concluded that urgent endoscopy was an independent predictor of a lower mortality rate. Although these results differ from our findings that urgent endoscopy is not associated with mortality, the study included patients with a GBS of >7 (not 12), and more than half of the patients (571 of 961) underwent urgent endoscopy. Although less severe patients who undergo urgent endoscopy might bias the mortality rate, mortality was associated with cancer and cirrhosis, indicating underlying comorbidity aggravation, which we agree can be reduced by urgent endoscopy.

Our study has the following limitations. First, comorbidity aggravation may be inconsistent and subjective since attending physicians identify comorbidity aggravation based on clinical judgment. Additionally, such judgments require selection from various aggravation degrees. However, we prospectively approached the patients' conditions, which might have compensated for this limitation. Second, because GBS has a well-known limitation in predicting re-bleeding, classifying risk groups by GBS based on the re-bleeding rate may cause selection bias. Accordingly, the mean re-bleeding rate differences in the low-risk group may be not reliable. However, because we adjusted for other factors that affect re-bleeding, such as PPI administration and visualization during endoscopy, our results can still explain the re-bleeding rate by risk group. Third, other confounding factors such as endoscopist competence and date of index endoscopy (weekday or weekend) were not analyzed in our study. The success rate of primary endoscopic intervention could have effect on the clinical outcomes such as rebleeding and hospital stay. Further promising pre-endoscopic scoring systems for predicting clinical outcomes are needed to enable precise risk stratification. Fourth, selection bias risk cannot be avoided in a retrospective study because of the large number of subjects. Additionally, to compare the prognosis between two groups based on endoscopy timing, the two groups should not differ in baseline characteristics. To strengthen the conclusions' persuasive power, propensity score matching is necessary. However, this was an observational study reflecting clinical practice and involved real data without statistical manipulation.

Conclusion

For the NVUGIB management in low-risk patients, delayed endoscopy may be sufficient. Although it did not influence mortality in this study, urgent endoscopy may be an option for NVUGIB management in high-risk patients with major comorbidities.

Authors' Contribution

Conceptualization: Seong Woo Jeon. Data curation: Ju Yup Lee. Formal analysis: Ju Yup Lee. Investigation: Joong Goo Kwon. Methodology: Seong Woo Jeon. Project administration: Seong Woo Jeon. Supervision: Seong Woo Jeon. Validation: Si Hyung Lee. Visualization: Ho Jin Lee. Writing—original draft: Seong Woo Jeon. Writing—review & editing: Ho Jin Lee. Approval of final manuscript: all authors.

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