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Original Contribution

Delayed endoscopy is associated with increased mortality in upper gastrointestinal hemorrhage

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ABSTRACT

Objectives: To determine the association between delayed (>24 h) endoscopy and hospital mortality in patients with upper gastrointestinal hemorrhage (UGIH).
Methods: We retrospectively analyzed all adult patients with UGIH who underwent endoscopy in a single emergency room for 2 years. The primary exposure was defined as >24 h from the ED visit to the first endoscopy. The primary outcome was defined as all cause hospital mortality. Secondary outcomes were intensive care unit admission rate, ED length of stay, and hospital length of stay.
Results: Among 1101 patients enrolled, 898 received endoscopy within 24 h (early group) and 203 received endoscopy after 24 h (delayed group). The hospital mortality of early and delayed group was 2.8% and 6.4%, respectively (unadjusted relative risk [RR] 2.30: 95% CI, 1.20–4.42, p = 0.012). This was significant after adjusting covariates including AIMS65 and Glasgow-Blatchford score (adjusted RR 2.23: 95% CI, 1.18–4.20, p = 0.013). Intensive care unit admission rate was not different between two groups. ED and hospital length of stay were significantly longer in delayed group.
Conclusions: Endoscopy performed after 24 h was associated with increased hospital mortality in UGIH. Patients in the delayed group stayed longer in the ED and in the hospital.

1. Introduction

Upper gastrointestinal hemorrhage (UGIH) is one of the most common causes of emergency department (ED) visit. The prevalence of UGIH is 20 to 60 per 100,000 population, and the mortality rate is 5 to 10% [1]. Esophagogastroduodenoscopy (EGD) is the gold standard procedure for UGIH because it can diagnose the etiology and can also provide the hemostasis [2].

Theoretically, early EGD can be beneficial in both mild and severe cases. First, it enables faster diagnosis and preventing unnecessary hospitalization. Secondly, it can provide earlier hemostasis leading to a better prognosis. Current guidelines recommend that EGD should be performed within 24 h [3-5]. However, in holidays and weekend, EGD may be delayed (time to EGD surpassing 24 h since initial ED visit) [6]. Previous observational studies which have evaluated the benefit of early (within 24 h) EGD did not show a significant difference in mortality [7,8]. Also, most observational studies concerning the timing of endoscopy did not use the validated risk scores such as Glasgow-Blatchford and AIMS65 score [9,10].

We hypothesized that delayed EGD (performed after 24 h of ED visit) would increase the hospital mortality after adjusting risk scores in UGIH.

2. Methods

2.1. Study design and setting

This was a retrospective observational study performed in a single academic hospital ED. EGD is readily available from 08:00 to 18:00 during the weekday. However, on a weekday night time, weekend, and holidays, only emergency EGD is performed in patients requiring urgent management.

This study was approved by the institutional review board (IRB No. H-1802-048-921) and was exempt from patient's informed consent.

2.2. Participants

All ED visits from January 1, 2015 to December 31, 2016 were identified using electronic hospital information system (HIS). Patients who were ≥18 years old and who have received EGD during ED stay or subsequent hospital stay after ED visits were considered as eligible for the study enrollment.

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Chief complaints including the following terms were considered as having symptoms compatible with UGIH; "bleeding", "bloody", "hematemesis", "melena", "hematochezia", "anemia", "syncope", "fainting", "mental change", and "hypotension". On the other hand, chief complaints including following terms were considered as having symptoms not compatible with UGIH; "chest pain", "dyspnea", "fever", "jaundice", "palpitation", "sweating", and "general ache" and were excluded. Patients with corrosive ingestion or foreign body were categorized as injury and were excluded. Patients who underwent an endoscopic procedure such as endoscopic gastrostomy were also excluded. Finally, patients without discharge diagnosis compatible with UGIH were excluded. Discharge diagnosis in ICD 10 codes compatible with UGIH were as follows: C15, Malignant neoplasm of esophagus; C16, Malignant neoplasm of stomach; C17.0, Malignant neoplasm of duodenum; C26.9, Gastrointestinal stromal tumor; I86.4, Gastric varix; I98.3, Esophageal varix with bleeding; K25, Gastric ulcer; K26, Duodenal ulcer; K27, Peptic ulcer; K29.0, Acute hemorrhagic gastritis; K31.7, Polyp of stomach and duodenum; K31.8, Gastric angiodysplasia; K920, Hematemesis; K921, Melena; K922, Gastrointestinal hemorrhage.

2.3. Data collection

The hospital data management staff who did not know the study hypothesis extracted the data from the HIS according to the conditions suggested by the researchers. We reviewed the data coded in the excel sheet. Additional chart reviews were performed in only 10 cases with abnormal vital signs (for example, blood pressure was recorded as −1). The following data were obtained: ED visiting time, chief complaints as a text format, age, gender, underlying diseases (hypertension, diabetes, chronic liver disease), triage vital signs (systolic blood pressure, heart rate), mental status as AVPU (Alert, Verbal, Pain, and Unresponsive) scale (VPU were categorized as altered mentation), initial laboratory results (hemoglobin, blood urine nitrogen, serum albumin, and prothrombin time international normalized ratio [PT INR]), the amount of transfused pack red blood cell (RBC) during subsequent 3 days, time to EGD, therapeutic intervention as hemostasis or varix ligation, secondary EGD, alternative modalities (Computed tomography [CT] angiography, conventional angiography, and operation), ED disposition (discharge, admission [ward or intensive care unit], transfer to another hospital, and ED death), ED length of stay, hospital mortality, hospital length of stay, and discharge diagnosis in ICD 10 codes.

AIMS65 and Glasgow-Blatchford scores (GBS) were calculated using original categories. Chief complaints, age, gender, chronic liver disease, systolic blood pressure, heart rate, mental status, hemoglobin, blood urine nitrogen, serum albumin, and PT INR were used. However, cardiac failure was not used for GBS calculation since the information about cardiac failure was not routinely recorded in ED triage.

2.4. Exposure variables

The primary exposure was time to first EGD after 24 h of ED visit. Patients were categorized into early group (time to EGD was less than or equal to 24 h) or delayed group (time to EGD was >24 h).

2.5. Outcome measures

The primary outcome was defined as all-cause hospital mortality.

Secondary outcomes were as follows; intensive care unit admission, ED length of stay, and Hospital length of stay.

2.6. Statistical analysis

Continuous variables were presented as medians with interquartile ranges (IQR), and categorical variables were presented as percent frequencies of occurrences. The Wilcoxon rank-sum test was used to compare continuous variables, and the chi-square test or Fisher's exact test was used to compare categorical variables, as appropriate.

For primary outcome analysis, relative risk and odds ratio were calculated using modified Poisson and the logistic regression model, respectively [11]. An adjustment was performed using age, gender, visiting hour, AIMS65, and Glasgow-Blatchford score. Subgroup analysis was performed using visiting hour and risk scores. Secondary outcomes were ED length of stay, and hospital length of stay. Kaplan-Meier survival analysis with log-rank test was performed to show the mortality difference and the length of stay.

Throughout the analysis, two-tailed p values < 0.05 were considered to indicate statistical significance. All analyses were performed using Stata version 13.1 (Stata Corp, College Station, TX).

3. Results

3.1. Participants

During the study period, 2092 patients who received EGD were identified. After excluding 991 patients (no symptoms compatible with UGIH, had injury such as foreign body, received the procedure such as endoscopic gastrostomy, without discharge diagnosis compatible with UGIH), 1101 patients were analyzed (Fig. 1).

3.2. Patients characteristics

Among 1101 patients, 898 (81.6%) received EGD within 24 h from ED presentation and 203 (18.4%) did not. Table 1 describes the characteristics of the patients in early and delayed group. The proportion of weekend and holidays visits was significantly higher in the delayed group than early group. Demographics (age and gender) and underlying diseases were not different between the two groups. Systolic blood pressure were not different, however heart rate was faster in delayed

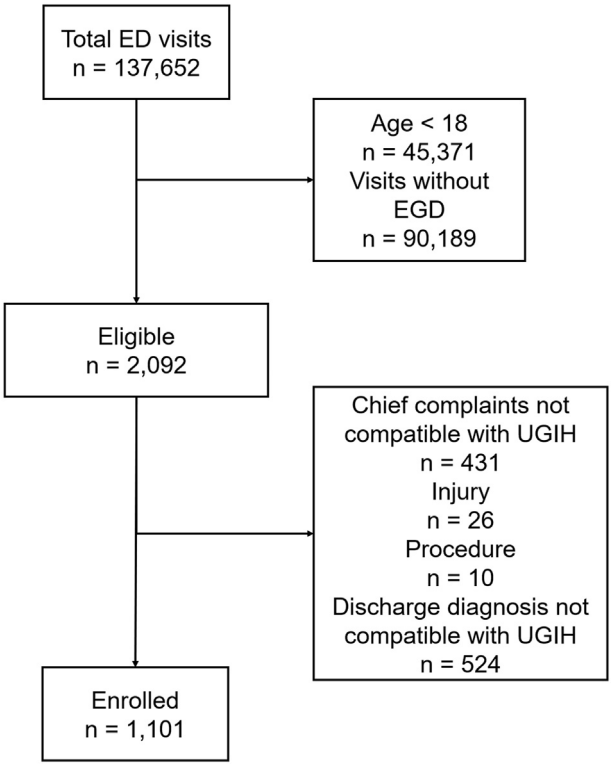

Fig. 1. Flowcharts describing enrollment. Abbreviations: ED, emergency department; EGD, esophagogastroduodenoscopy; UGIH, upper gastrointestinal hemorrhage.

Table 1
Characteristics of the patients.

Characteristics	Early group (n = 898)	Delayed group (n = 203)	p value
Visiting hours, n. (%)			
Weekday, on-hour (08:00–18:00)	572 (63.7)	84 (41.4)	<0.001
Weekday, off-hour (18:00–08:00)	234 (26.1)	21 (10.3)	
Weekend and holidays	92 (10.2)	98 (48.3)	
Demographics			
Age, median (IQR), year	65 (55–75)	64 (55–74)	0.685
Age ≥ 65, n. (%), year	456 (50.8)	98 (48.3)	0.519
Male gender, n. (%)	594 (66.2)	134 (66.0)	0.970
Underlying diseases, n. (%)			
Hypertension	224 (24.9)	56 (27.6)	0.435
Diabetes	188 (20.9)	50 (24.6)	0.248
Chronic liver disease	172 (19.2)	41 (20.2)	0.734
Initial vital signs, median (IQR)			
Systolic blood pressure, mm Hg	124 (109–143)	124 (105–139)	0.394
Systolic blood pressure < 90 mm Hg, n. (%)	61 (6.8)	14 (6.9)	0.958
Heart rate, beat/min	90 (76–104)	95 (85–110)	<0.001
Altered mentation, n. (%)	45 (5.0)	22 (10.8)	0.002
Initial lab. results, median (IQR)			
Hemoglobin, g/dL	9.3 (7.4–11.2)	9.5 (7.5–12)	0.180
Blood urine nitrogen, mg/dL	24 (16–38)	25 (16–42)	0.609
Albumin, g/dL	3.3 (2.9–3.8)	3.2 (2.8–3.7)	0.041
PT INR	1.13 (1.03–1.32)	1.17 (1.05–1.45)	0.007
Risk scores			
AIMS65 score, median (IQR)	1 (0–2)	1 (0–2)	0.058
AIMS65 score ≥ 1, n. (%)	628 (69.9)	146 (71.9)	0.576
AIMS65 score ≥ 2, n. (%)	240 (26.7)	71 (35.0)	0.018
Glasgow-Blatchford score, median (IQR)	8 (5–11)	8 (5–10)	0.510
Glasgow-Blatchford score ≥ 2, n. (%)	811 (90.3)	183 (90.2)	0.943
Glasgow-Blatchford score ≥ 6, n. (%)	635 (70.7)	140 (69.0)	0.622
RBC transfusion			
1st day, n. (%)	341 (38.0)	61 (30.1)	0.034
Total volume, ml, median (IQR)	800 (640–960)	800 (640–1200)	0.951
1st to 3rd day, n. (%)	421 (46.9)	88 (43.4)	0.362
Total volume, ml, median (IQR)	800 (640–1200)	800 (640–1200)	0.447
Endoscopy			
Time to 1st endoscopy, median (IQR), hours	5.8 (3.3–15.3)	39.4 (26.7–48.6)	<0.001
Endoscopy only, n. (%)	648 (72.2)	164 (80.8)	0.012
Hemostasis, n. (%)	111 (12.4)	10 (4.9)	0.002
Varix ligation, n. (%)	141 (15.7)	29 (14.3)	0.614
2nd Endoscopy, n. (%)	34 (3.8)	3 (1.5)	0.129[a]
Alternative modalities, n. (%)			
CT angiography	232 (25.8)	81 (39.9)	<0.001
Conventional angiography	76 (8.5)	8 (3.9)	0.028
Operation	1 (0.1)	0	NA
ED disposition, n. (%)			
Discharge	201 (22.4)	23 (11.3)	0.001
Admission	677 (75.4)	170 (83.7)	
Transfer to another hospital	17 (1.9)	9 (4.4)	
ED death	3 (0.3)	1 (0.5)	

Abbreviations: IQR, interquartile range; PT INR, prothrombin time international normalized ratio; CT, computed tomography; NA, not applicable.
[a] Fisher's exact test was used.

group. Patients with altered mentation were more frequent in delayed group.

In laboratory results, hemoglobin concentration and blood urine nitrogen level were not different. Serum albumin was lower, and PT INR was higher in delayed group. There was no difference in the AIMS65 score and the Glasgow-Blatchford score between the two groups. The high-risk group with AIMS65 score 2 or more was more frequent in the delayed group. Proportion of patients who received RBC transfusion was significantly higher in early group at 1st day. However, total volume of RBC in patients who received RBC transfusion were not different between the two groups. More patients in the early group received therapeutic interventions such as hemostasis, and conventional angiography. In contrast, CT angiography were performed more in the delayed group. More patients in the early group were discharged at ED.

3.3. Study outcomes

Hospital mortality rate in delayed group was 6.4% (13/203), which was significantly higher than early group (2.8%, 25/898) (Table 2). Unadjusted relative risk of delayed endoscopy was 2.30 (95% CI, 1.20–4.42, p = 0.012). After adjusting age, gender, visiting hour, AIMS65, and Glasgow-Blatchford score, relative risk of delayed group was 2.23 (95% CI, 1.18–4.20, p = 0.013). Unadjusted and adjusted odds ratio of delayed endoscopy were 2.39 (95% CI, 1.20–4.76, p = 0.013) and 2.45 (95% CI, 1.14–5.31, p = 0.022), respectively. Kaplan-Meier survival analysis showed increased hospital mortality in delayed group (Fig. 2(A)).

The mortality of delayed group of all subgroup analysis tended to be higher than early group. Especially, the mortality of delayed group was significantly higher in high risk patients (AIMS65 score 1 or more and Glasgow-Blatchford score 2 or more).

ED length of stay was longer in delayed group. This result was consistent in both discharged and hospitalized patients. Hospital length of stay was significantly longer in the delayed group (Table 2 and Fig. 2 (B)).

4. Discussion

In this study, we have found that endoscopy after 24 h of presentation was associated with increased mortality in patients with UGIH. This association was significant after adjusting risk scores of AIMS65

Table 2
Study outcomes.

Outcomes	Early group (n = 898)	Delayed group (n = 203)	p value
Primary outcome			
Hospital mortality, n. (%)	25 (2.8)	13 (6.4)	0.011
Unadjusted relative risk, (95% CI)[a]	2.30 (1.20–4.42)		0.012
Adjusted relative risk, (95% CI)[b]	2.23 (1.18–4.20)		0.013
Unadjusted odds ratio, (95% CI)[a]	2.39 (1.20–4.76)		0.013
Adjusted odds ratio, (95% CI)[b]	2.45 (1.14–5.31)		0.022
Subgroup analysis			
Weekday visits, n	806	105	
Hospital mortality, n. (%)	24 (3.0)	7 (6.7)	0.077[c]
Weekend and holidays, n	92	98	
Hospital mortality, n. (%)	1 (1.1)	6 (6.1)	0.119[c]
AIMS65 score ≥ 1, n	628	146	
Hospital mortality, n. (%)	20 (3.2)	13 (8.9)	0.005[c]
Glasgow-Blatchford score ≥ 2, n	811	183	
Hospital mortality, n. (%)	25 (3.1)	13 (7.1)	0.010
Secondary outcomes			
ICU admission, n. (%)	17 (1.9)	2 (1.0)	0.370
ED length of stay, median (IQR), hours	25.3 (10.7–35.2)	47.9 (30.1–55.9)	<0.001
Discharge at ED (n = 224)	22.8 (9.3–35.8)	50.8 (33.4–53.3)	<0.001
Admission (n = 847)	26.2 (11.4–35.1)	46.6 (29.4–55.9)	<0.001
Hospital length of stay, median (IQR), days	3.0 (1.8–4.9)	4.1 (2.9–7.7)	<0.001

Abbreviations: CI, confidence intervals; ED, emergency department; ICU, intensive care unit.
[a] Modified Poisson model or logistic regression analysis was used to estimate the relative risk and odds ratio with confidence intervals.
[b] Age, gender, visiting hours, AIMS65 and Glasgow-Blatchford score were included in the modified Poisson or multivariate logistic regression model.
[c] Fisher's exact test was used.

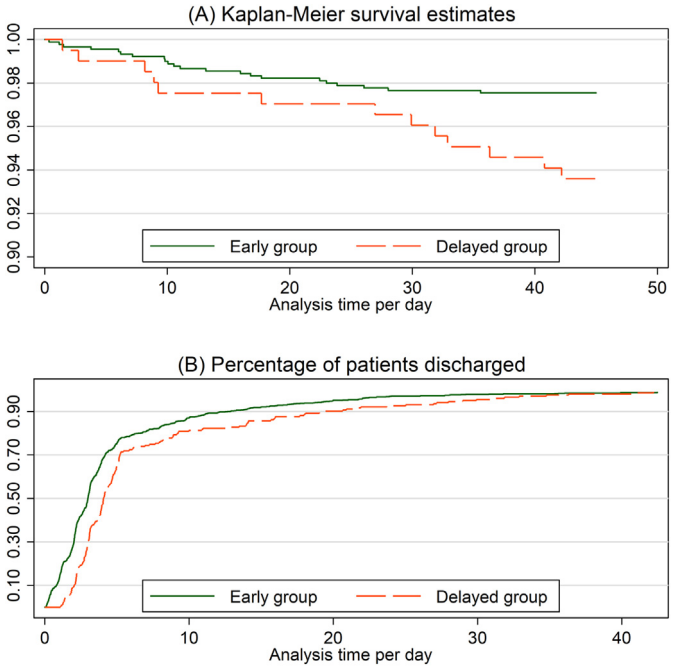

Fig. 2. (A) Kaplan-Meier survival graph comparing hospital mortality between early and delayed group. The survival rate was significantly different between two groups (log-rank test $p = 0.004$) (B) Kaplan-Meier curve presenting the percentage of patients who were discharged in early and delayed group. The rate of discharged patients was significantly higher in the early group (log-rank test $p < 0.001$).

and Glasgow-Blatchford score. Patients in delayed group stayed significantly longer in the ED and the hospital.

Visiting hours were significantly associated with delayed EGD. Over half of visits during weekend and holidays (98/190, 51.6%) received EGD after 24 h. This can be easily expected because EGD is not readily available during these periods.

There are no prospective controlled trials which has compared the early and delayed EGD in patients with UGIH. Also, there was no mortality difference in previous observational studies [7,8]. One study has shown that the surgery rate could be reduced in the early group [7] and another study has reported that the early endoscopy could reduce the rate of re-bleeding and the need for surgery [8]. In our study, the surgery was performed in only one patient. This is the result of the development of selective angiography in gastrointestinal hemorrhage [12]. Other therapeutic interventions such as hemostasis, and conventional angiography were performed more frequently in early group. Early group received RBC more frequently. However, the mortality was higher in delayed group.

CT angiography is readily available in many EDs and may provide the etiology of UGIH [13]. However, increased use of CT angiography in delayed group did not result in subsequent therapeutic interventions such as conventional angiography. This might be the result of looking for another modality because the endoscopy was delayed.

Delayed endoscopy not only increased hospital mortality but also prolonged ED and hospital length of stay. Median ED length of stay in this study was 27.7 h since the ED was suffering from overcrowding during the study period. Early endoscopy may accelerate disposition decisions and shorten ED and hospital length of stay. Early disposition decision is more important in overcrowded ED like ours.

In previous studies, more severe patients were included in the early group [7,8]. This difference in severity may have affected on the negative mortality outcomes. In contrast to previous studies, delayed endoscopy was significantly associated with hospital mortality in this study. This might be due to the fact that more patients with chronic liver disease were enrolled in this study (19.3% vs 4%).

This study has several limitations. First, this study was a retrospective analysis performed in a single emergency center. Although we tried to obtain as much objective data as possible from HIS, we could not overcome the potential bias of a retrospective study. Thus, unmeasured characteristics of delayed group might have effect on the hospital outcome even after adjusting the severity of UGIH. For example, endoscopy may be delayed if the patient is too unstable to perform endoscopy. Also, medical services other than endoscopy such as conventional angiography are less available during weekend and holidays. Although we have adjusted the visiting hours in addition to demographics and severity score, many other confounding factors could have influenced the increased mortality. Second, overall mortality rate of this study was only 3.5% (38/1101). Although the mortality difference was statistically significant, only 7 less deaths in 203 patients of delayed group would have made the mortality identical between two groups. Therefore, it should be cautious in interpreting the results of this study.

5. Conclusion

In this retrospective study, delayed EGD (performed after 24 h from initial ED presentation) was associated with increased mortality in UGIH patients. Patients in the delayed group stayed longer in the ED and in the hospital. Further studies are warranted to address the clinical consequences of the delayed endoscopy in ED patients with UGIH.

Declaration of interest

The authors declare that there are no conflicts of interest.

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