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Contents

ABOUT COVER

Editorial board member of *World Journal of Gastroenterology*, Wan-Long Chuang, MD, PhD, Doctor, Professor, Hepatobiliary Division, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung 807, Taiwan

AIMS AND SCOPE

World Journal of Gastroenterology (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, online ISSN 2219-2840, DOI: 10.3748) is a peer-reviewed open access journal. *WJG* was established on October 1, 1995. It is published weekly on the 7th, 14th, 21st, and 28th each month. The *WJG* Editorial Board consists of 642 experts in gastroenterology and hepatology from 59 countries.

The primary task of *WJG* is to rapidly publish high-quality original articles, reviews, and commentaries in the fields of gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, hepatobiliary surgery, gastrointestinal oncology, gastrointestinal radiation oncology, gastrointestinal imaging, gastrointestinal interventional therapy, gastrointestinal infectious diseases, gastrointestinal pharmacology, gastrointestinal pathophysiology, gastrointestinal pathology, evidence-based medicine in gastroenterology, pancreatology, gastrointestinal laboratory medicine, gastrointestinal molecular biology, gastrointestinal immunology, gastrointestinal microbiology, gastrointestinal genetics, gastrointestinal translational medicine, gastrointestinal diagnostics, and gastrointestinal therapeutics. *WJG* is dedicated to become an influential and prestigious journal in gastroenterology and hepatology, to promote the development of above disciplines, and to improve the diagnostic and therapeutic skill and expertise of clinicians.

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World Journal of Gastroenterology (*WJG*) is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central and Directory of Open Access Journals. The 2018 edition of Journal Citation Reports® cites the 2017 impact factor for *WJG* as 3.300 (5-year impact factor: 3.387), ranking *WJG* as 35th among 80 journals in gastroenterology and hepatology (quartile in category Q2).

EDITORS FOR THIS ISSUE

ORIGINAL ARTICLE

Retrospective Cohort Study

Timing of upper gastrointestinal endoscopy does not influence short-term outcomes in patients with acute variceal bleeding

Jeong-Ju Yoo, Young Chang, Eun Ju Cho, Ji Eun Moon, Sang Gyune Kim, Young Seok Kim, Yun Bin Lee, Jeong-Hoon Lee, Su Jong Yu, Yoon Jun Kim, Jung-Hwan Yoon

Jeong-Ju Yoo, Sang Gyune Kim, Young Seok Kim, Department of Gastroenterology and Hepatology, Soonchunhyang University school of Medicine, Bucheon 14584, South Korea

Young Chang, Eun Ju Cho, Yun Bin Lee, Jeong-Hoon Lee, Su Jong Yu, Yoon Jun Kim, Jung-Hwan Yoon, Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul 03080, South Korea

Ji Eun Moon, Department of Biostatistics, Clinical Trial Center, Soonchunhyang University Bucheon Hospital, Bucheon 14584, South Korea

ORCID number: Jeong-Ju Yoo (0000-0002-7802-0381); Young Chang (0000-0001-7752-7618); Eun Ju Cho (0000-0002-2677-3189); Ji Eun Moon (0000-0002-0887-703X); Sang Gyune Kim (0000-0001-8694-777X); Young Seok Kim (0000-0002-7113-3623); Yun Bin Lee (0000-0002-3193-9745); Jeong-Hoon Lee (0000-0002-0315-2080); Su Jong Yu (0000-0001-8888-7977); Yoon Jun Kim (0000-0001-9141-7773); Jung-Hwan Yoon (0000-0002-9128-3610).

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Abstract

AIM

To examine the association between the timing of endoscopy and the short-term outcomes of acute variceal bleeding in cirrhotic patients.

METHODS

This retrospective study included 274 consecutive patients admitted with acute esophageal variceal bleeding of two tertiary hospitals in Korea. We adjusted confounding factors using the Cox proportional hazards model and the inverse probability weighting (IPW) method. The primary outcome was the mortality of patients within 6 wk.

RESULTS

A total of 173 patients received urgent endoscopy (*i.e.*, ≤ 12 h after admission), and 101 patients received non-urgent endoscopy (> 12 h after admission). The 6-wk mortality rate was 22.5% in the urgent endoscopy group and 29.7% in the non-urgent endoscopy group, and there was no significant difference between the two groups before (P = 0.266) and after IPW (P = 0.639). The length of hospital stay was statistically different between the urgent group and non-urgent group (P = 0.033); however, there was no significant difference in the in-hospital mortality rate between the two groups (8.1% *vs* 7.9%, P = 0.960). In multivariate analyses, timing of endoscopy was not associated with 6-wk mortality (hazard ratio, 1.297; 95% confidence interval, 0.806-2.089; P = 0.284).

CONCLUSION

In cirrhotic patients with acute variceal bleeding, the timing of endoscopy may be independent of short-term mortality.

Key words: Cirrhosis; Endoscopy; Upper gastrointestinal bleeding; Gastroesophageal varices; Timing

Core tip: Most guidelines recommend performing endoscopy for acute variceal bleeding within 12 h. However, the evidence level for this recommendation is very low. We found that, after inverse probability weighting matching, compared to non-urgent endoscopy, performing endoscopy within 12 h of admission (so-called urgent endoscopy) was not associated with short-term prognosis, including overall survival at 6 wk or transplant-free survival at 6 wk. Rather, age, hepatocellular carcinoma, model for end-stage liver disease score, and degree of ascites were related to short-term mortality. These results indicate that, in cirrhotic patients with acute variceal bleeding, the timing of endoscopy does not appear to be associated with short-term prognosis.

INTRODUCTION

Variceal bleeding is a common complication of cirrhosis of the liver, and in patients with cirrhosis, is found to be the cause of 60%-65% of bleeding episodes[1]. It increases the risk of mortality by approximately 15%-20%. Many guidelines recommend a standardized treatment of acute variceal bleeding[2-5]. Endoscopic procedures and endoscopic hemostasis techniques, *e.g.*, band ligation, are considered very important in the treatment of such patients[6], with most guidelines recommending that emergency endoscopy be performed within 12 h of hospital arrival[4-6].

However, this recommendation appears to be based on "expert opinion", rather than on the level of evidence, which is in fact very low. For example, one survey showed significant variability in gastoenterologists' opinion of the timing of emergency endoscopy following variceal bleeding[7]. Moreover, there is little related research to date to support this current recommendation of endoscopy within 12 h of hospital arrival[8,9]. However, providing better evidence by clinically performing a randomized controlled trial on these acutely ill patients is problematic, because of their unstable vital signs and the ethical problems that would arise from this type of study.

Compared to other medical treatments such as vasoactive agents, endoscopy is a relatively invasive procedure and both the risk and benefit to the patient need to be considered. If unnecessary endoscopies are frequently performed, medical staff fatigue may increase dramatically, and so may the medical costs[10]. Moreover, if endoscopy is performed too early, the examination may be may not be adequate; for example it may be marred by remnant blood clots *etc*. As well, the risk of a procedure-related complication tends to increase when endoscopy is performed too early in patients with unstable condition compared to when performed in a more stable state[10,11]. To date, a gold standard recommended timing of endoscopy in patients with acute variceal bleeding has not been clearly determined.

The aim of this study was to examine the association between the timing of endoscopy and clinical outcomes in acute esophageal variceal bleeding.

MATERIALS AND METHODS

Patients

We collected the data of cirrhotic patients undergoing routine clinical care in either of two tertiary hospitals

(Seoul National University Hospital and Soon Chun Hyang University Bucheon Hospital) between January 2011 and December 2015. The inclusion criteria were as follows: (1) Cirrhotic patients admitted *via* the emergency room (ER) with upper gastrointestinal bleeding (UGIB), and diagnosed through endoscopy with acute variceal bleeding; and (2) aged over 19 years. Exclusion criteria were as follows: (1) Patients who did not undergo endoscopic examination during ER stay (*n* = 38); (2) UGIB from other than variceal bleeding (*e.g.*, peptic ulcer bleeding, portal hypertensive gastropathy bleeding) (*n* = 165); or (3) if endoscopy had been performed within 7 d prior to admission (*n* = 7). In total, 484 patients met the inclusion criteria and 210 patients were excluded as above. Finally, 274 patients were analyzed.

Standard of care and endoscopic procedure
When a cirrhotic patient with UGIB arrived at the ER of each hospital, adequate fluid resuscitation, a prophylactic antibiotic, and a vasoactive drug with terlipressin were immediately administered at the time of admission. If peptic ulcer bleeding could not be ruled out, a proton pump inhibitor was also administrated. An emergency medical specialist first examined the patient, and consulted a gastrointestinal (GI) specialist about whether an endoscopy was to be performed. Then, the GI specialist determined the timing of the endoscopy, considering each patient's age, presence of comorbidities such as renal failure or cardiopulmonary disease, presence of hepatic encephalopathy, hemodynamic instability, and laboratory abnormalities including anemia, lactic acidosis and coagulopathy. If patients did not exhibit poor clinical factors or they had signs of hepatic encephalopathy more than grade Ⅲ, delayed endoscopic examination was considered. (In both hospitals, a GI specialist with technical expertise in the use of endoscopic devices is on call 24 h a day, 7 d a week.) Therapeutic endoscopy was performed using standard video-endoscopes (GIF-Q260 or GIF-Q290; Olympus, Tokyo, Japan). When EVL failed, salvage treatments including endoscopic variceal obturation (EVO) using n-butyl-2-cyanoacrylate (NBC), insertion of a Sengstaken-Blakemore (SB) tube, transjugular intrahepatic portosystemic shunt, variceal embolization, or a combination of multiple treatment modalities were performed. When EVO was performed, NBC (Histoacryl®; B. Braun Dexon, Spangenberg, Germany) was mixed with ethiodized oil (Lipiodol; Guerbert, Roissy, France) and was injected as a bolus dose of 0.5-2 mL, depending on the amount of bleeding.

Data collection
Two independent reviewers (Yoo JJ and Chang Y), each with more than 5 years of endoscopic experience, screened medical records and endoscopic reports to confirm that each case was of a true acute gastroesophageal variceal bleeding. If a patient was admitted more than once during the study period due to variceal bleeding, the earliest visit was selected for inclusion in the analysis. Demographics, relevant medical history, any comorbid conditions, and relevant laboratory findings at the time of admission were collected. Two widely-studied UGIB prognostic scores of each of the patients, namely the Glasgow-Blatchford score (GBS) and the Rockall score, were also calculated[12,13]. If the patient had died during the study period, the cause of death was evaluated from hospital records, where possible.

Definitions
Time to endoscopy was defined as the time interval from the hospital arrival to the initial endoscopic examination[14]. Urgent endoscopy was defined according to the guidelines as an endoscopic examination performed within 12 h of admission, and non-urgent endoscopy defined as one performed after 12 h[5].

The primary outcome for this study was the 6-wk mortality rate following variceal bleeding. The secondary outcomes were: 6-wk mortality or transplantation rates, hospital admission duration, in-hospital mortality, and re-bleeding rate.

Statistical analysis
Only the patients with complete data were analyzed in this study. Frequencies with percentages and means with standard deviations were used for descriptive statistics. Statistical differences between the groups were investigated using the χ^2 test or Fisher's exact test for categorical variables and the Student's *t* test or Mann-Whitney *U* test for continuous variables. Cumulative 6-wk survival and transplant-free survival (TFS) rates after acute variceal bleeding were estimated using the Kaplan-Meier method, and differences between the curves were compared using the log-rank test. In patients with loss to follow-up, the data were censored on the last date on which their survival status was known. The effect of endoscopic timing on clinical outcomes was assessed using the Cox proportional hazards regression model. If multicollinearity occurred between the individual components in the univariate analysis, only the most relevant prognostic parameter was included in the final multi-variable model. The inverse probability weighting method based on propensity score was applied so as to correct baseline differences between the two groups (urgent endoscopy *vs* non-urgent endoscopy). A *P*-value less than 0.05 was considered significant. Hazard ratios (HRs) and 95% confidence intervals (CIs) were also calculated. All statistical analyses were performed using R (version 3.3.3, The R Foundation for Statistical Computing, Vienna, Austria), or PASW version 18.0 statistical software (SPSS Inc.; Chicago, IL, United States).

RESULTS

Baseline characteristics
The baseline characteristics of the patients enrolled in the study are reported in Table 1. The mean age of the

Table 1 Baseline characteristics of patients before and after inverse probability weighting *n* (%)

Characteristics	Unweighted				Inverse probability weighting			
	All patients (*n* = 274)	Urgent endoscopy (*n* = 173)	Non-urgent endoscopy (*n* = 101)	*P* value	All patients (*n* = 272)	Urgent endoscopy (*n* = 172)	Non-urgent endoscopy (*n* = 100)	*P* value
Demographics								
Age (yr)	58.05 ± 12.10	57.62 ± 12.09	58.77 ± 12.22	0.45	58.14 ± 0.85	58.17 ± 1.03	58.10 ± 1.34	0.971
Sex (male)	207 (75.5)	128 (74.0)	79 (78.2)	0.469	205 (74.6)	127 (37.2)	78 (37.4)	0.956
Hepatocellular carcinoma	149 (54.4)	97 (56.1)	52 (51.5)	0.452	148 (54.8)	97 (27.8)	51 (27.0)	0.830
Prior variceal upper GI bleeding	179 (65.3)	110 (63.6)	69 (68.3)	0.511	178 (65.7)	109 (32.3)	69 (33.5)	0.713
Prior non-variceal upper GI bleeding	8 (2.9)	2 (1.2)	6 (5.9)	0.055	8 (2.9)	2 (1.4)	6 (1.5)	0.890
Initial hepatic encephalopathy				< 0.001				0.939
None	241 (88.0)	164 (94.8)	77 (76.2)		239 (88.6)	163 (44.5)	76 (44.4)	
Grade Ⅰ-Ⅱ	16 (5.8)	5 (2.9)	11 (10.9)		16 (5.4)	5 (2.5)	11 (2.9)	
Grade Ⅲ-Ⅳ	17 (6.2)	4 (2.3)	13 (12.9)		17 (5.7)	4 (2.6)	13 (3.1)	
Initial ascites				0.067				0.994
None	111 (40.5)	77 (44.5)	34 (33.7)		111 (41.1)	77 (20.3)	34 (20.8)	
Mild	77 (28.1)	50 (28.9)	27 (26.7)		76 (29.4)	49 (14.7)	27 (14.7)	
Moderate to severe	86 (31.4)	46 (26.6)	40 (39.6)		85 (29.5)	46 (14.6)	39 (14.9)	
Etiology				0.985				0.930
HBV	137 (50.0)	86 (49.8)	51 (50.5)		136 (49.7)	86 (24.4)	50 (25.33)	
HCV	25 (9.1)	16 (9.2)	9 (8.9)		25 (9.4)	16 (5.4)	9 (4.0)	
Alcohol	69 (25.2)	43 (24.9)	26 (25.7)		68 (24.0)	42 (12.3)	26 (12.7)	
Others	43 (15.7)	28 (16.2)	15 (14.9)		43 (16.0)	28 (8.0)	15 (8.0)	
Vital signs								
Systolic blood pressure (mm Hg)	117 ± 26	116 ± 26	120 ± 26	0.221	118 ± 2	116 ± 2	119 ± 3	0.408
Heart rate (beat/min)	95 ± 18	96 ± 19	94 ± 17	0.551	95 ± 1	95 ± 1	95 ± 2	0.827
Laboratory values								
Hemoglobin	9.2 ± 2.5	9.0 ± 2.5	9.6 ± 2.5	0.044	9.1 ± 0.2	8.8 ± 0.2	9.3 ± 0.3	0.105
Platelet count (10^3/mL)	117 + 79	118 ± 78	114 ± 80	0.701	118 ± 5	119 ± 6	118 ± 8	0.917
Total bilirubin	3.8 ± 5.8	3.5 ± 5.3	4.5 ± 6.5	0.148	3.7 ± 0.4	3.6 ± 0.5	3.8 ± 0.5	0.817
Serum albumin	2.9 ± 0.6	2.9 ± 0.6	2.9 ± 0.7	0.702	3.0 ± 0.1	3.0 ± 0.1	4.0 ± 0.1	0.736
Prothromin time (INR)	1.6 ± 1.8	1.4 ± 0.6	1.8 ± 2.9	0.046	1.6 ± 0.1	1.5 ± 0.1	1.7 ± 0.2	0.157
Serum creatinine	1.3 ± 1.5	1.4 ± 1.8	1.2 ± 1.0	0.24	1.2 ± 0.1	1.4 ± 0.1	1.1 ± 0.1	0.07
MELD score	15.9 ± 7.8	15.4 ± 6.9	16.9 ± 9.2	0.112	15.6 ± 0.5	15.6 ± 0.5	15.6 ± 0.8	0.964
Prognostic scores								
Glasgow-Blatchford score	9.1 ± 3.5	9.2 ± 3.3	9.1 ± 3.9	0.818	9.3 ± 0.2	9.3 ± 0.3	9.3 ± 0.4	0.907
Rockall score	3.9 ± 1.4	4.0 ± 1.4	3.6 ± 1.5	0.021	3.4 ± 0.1	3.9 ± 0.1	3.9 ± 0.2	0.875
Endoscopy								
Time to endoscopy, hours, median (IQR)	12.7 (2.8-16.5)	4.0 (2.1-6.8)	19.5 (15.0-35.5)	< 0.001	12.5 (2.8-16.4)	4.0 (2.2-6.8)	19.5 (15.1-35.4)	< 0.001

Data are expressed as mean ± standard deviation or number (percentage), unless otherwise stated. GI: Gastrointestinal; HBV: Hepatitis B virus; HCV: Hepatitis C virus; INR: International normalized ratio; MELD: Model for end-stage liver disease.

patients was 58.05 ± 12.10 years, and 75.5% (207) were male. The proportion of patients with hepatocellular carcinoma (HCC) was 54.4% (149). Sixty-five percent of the patients had experienced variceal bleeding prior to the study period. Chronic hepatitis B virus (HBV) infection was the most common etiology of cirrhosis, followed by alcohol use and other causes. Sixty percent of patients presented with any grade of ascites.

At the time of hospital arrival, the heart rate of the patients was found to be abnormally high, with an average of 95 beat per minute, and their mean systolic pressure was 116 ± 26 mmHg. They showed deteriorated liver function with a mean model for end-stage liver disease (MELD) score of 15.9 ± 7.8 points. The mean Glasgow-Blatchford score was 9.1 ± 3.5 points, suggesting a poor prognosis.

Patients underwent endoscopic examination at an average of 9.1 ± 3.5 h after arrival at the hospital. Based on the timing of the endoscopy, patients were divided into an urgent endoscopy group (< 12 h) and a non-urgent endoscopy group (≥ 12 h). The baseline characteristics of the two groups were similar and there was no significant difference in the MELD scores (15.4 ± 6.9 *vs* 16.9 ± 9.2; *P* = 0.088) between the two groups.

Impact of endoscopic timing on outcomes

The 6-wk mortality rate was 22.5% in the urgent endoscopy group and 29.7% in the non-urgent endoscopy group, and there were no significant differences between the two groups (*P* = 0.266, Figure 1). After IPW, the baseline characteristics were well balanced between the two groups (Tables 1). The IPW-adjusted analysis also showed that both groups did not differ in terms of the risk of death (*P* = 0.639). The 6-wk mortality or transplantation rate was slightly lower in the urgent group but with marginal significance (*P* = 0.060, Figure 2). However, after IPW there was no significant difference between the two groups (*P* = 0.532).

Table 2 Clinical outcomes of the patients *n* (%)

Outcomes	All patients (*n* = 274)	Urgent endoscopy (*n* = 173)	Non-urgent endoscopy (*n* = 101)	*P* value
Hospital admission duration, days, median (IQR)	4.0 (3.0-9.5)	4.0 (2.0-9.0)	4.0 (3.0-11.0)	0.033
In-hospital mortality	22 (8.0)	14 (8.1)	8 (7.9)	0.960
Re-bleeding rate	60 (21.9)	35 (20.2)	25 (24.8)	0.449
Six-week mortality	69 (25.2)	39 (22.5)	30 (29.7)	0.197
Liver transplantation	25 (9.1)	14 (8.1)	11 (10.9)	0.515

Data are expressed as number (percentage), unless otherwise stated. IQR: Interquartile range.
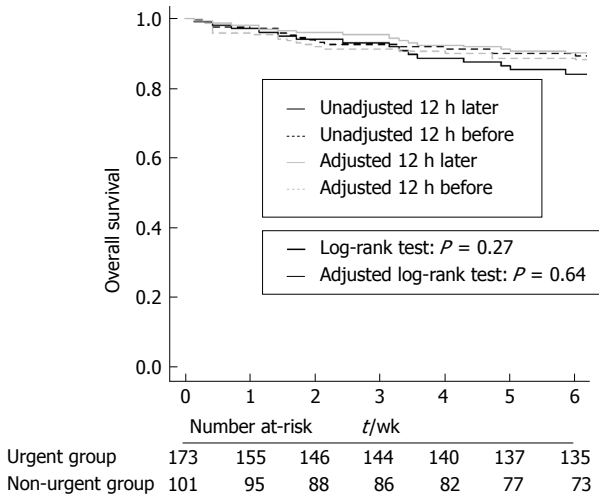

Figure 1 Comparison of 6-wk survival in the urgent and the non-urgent endoscopy groups. Kaplan-Meier survival plot stratified by timing of endoscopy of all patients. The dotted line indicates urgent endoscopy and the solid line indicates non-urgent endoscopy. The black line is the unadjusted cumulative survival graph before inverse probability weighting (IPW), and the gray line is the adjusted after the IPW correction.
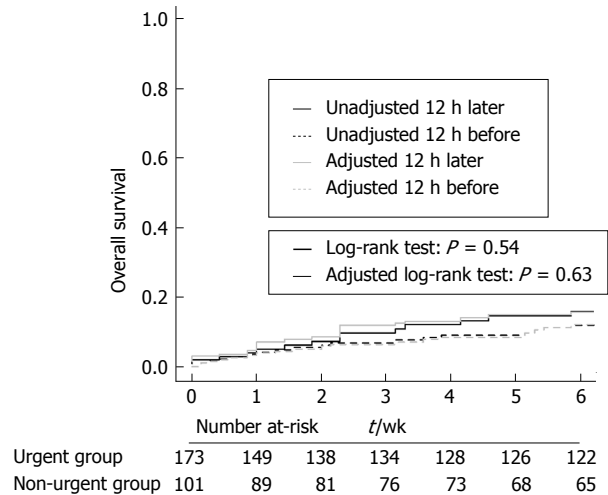

Figure 3 Comparison of 6-wk re-bleeding rate in the urgent and the non-urgent endoscopy groups. Kaplan-Meier survival plot stratified by timing of endoscopy of all patients. The dotted line indicates urgent endoscopy and the solid line indicates non-urgent endoscopy. The black line is the unadjusted cumulative graph before inverse probability weighting (IPW), and the gray line is the adjusted after the IPW correction.

Figure 2 Comparison of 6-wk transplant-free survival in the urgent and the non-urgent endoscopy groups. Kaplan-Meier survival plot stratified by timing of endoscopy of all patients. The dotted line indicates urgent endoscopy and the solid line indicates non-urgent endoscopy. The black line is the unadjusted cumulative graph before inverse probability weighting (IPW), and the gray line is the adjusted after the IPW correction.

Other clinical outcomes

Other clinical outcomes are described in Table 2. Although the median hospital admission duration was similar in both groups, significant differences observed in the mean rank scores (*i.e.*, Mann-Whitney *U* test), suggesting that the data for the non-urgent group were more right skewed (*P* = 0.033)[15]. However, there was no significant difference in the in-hospital mortality rate between the urgent group and the non-urgent group (8.1% *vs* 7.9%; *P* = 0.960).

The rate of variceal re-bleeding within 6 wk was 10.4% in the urgent group and 12.9% in the non-urgent group, which was statistically nonsignificant (*P* = 0.557). The Kaplan-Meier analysis of time to re-bleeding also showed no significant difference between the two groups either before or after IPW matching (*P* = 0.538 and 0.631, respectively; Figure 3).

Predictors of 6-wk mortality

Finally, we analyzed clinical predictors associated with 6-wk mortality (Table 3). Compared with non-urgent endoscopy, urgent endoscopy was not independently associated with short-term mortality [adjusted hazard ratio (aHR): 1.297; 95% confidence interval (CI): 0.806-2.089; *P* = 0.284). On the other hand, the following were independent risk factors of 6-wk mortality: advanced age (aHR: 1.035; 95%CI: 1.011-1.0059;

Table 3 Cox proportional hazards model for 6-wk mortality

Variable	Univariable		Multivariable	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age	1.037 (1.016-1.059)	< 0.001	1.035 (1.011-1.059)	0.004
Sex				
Female	1			
Male	0.946 (0.543-1.664)	0.845		
Etiology				
Non-viral	1		1	
Viral	0.536 (0.319-0.902)	0.019	0.683 (0.384-1.214)	0.194
Hepatocellular carcinoma	2.442 (1.439-4.142)	0.001	1.929 (1.072-3.469)	0.028
Diabetes Mellitus	0.535 (0.292-0.978)	0.042	0.423 (0.225-0.795)	0.008
Hypertension	0.994 (0.521-1.894)	0.984		
Prior variceal upper GI bleeding	0.916 (0.561-1.497)	0.726		
Prior non-variceal upper GI bleeding	3.92E-8 (0-INF)	0.996		
Systolic blood pressure	1.003 (0.994-1.012)	0.489		
Heart rate	1.005 (0.992-1.018)	0.477		
MELD score[1]	1.062 (1.041-1.083)	< 0.001	1.049(1.024-1.074)	< 0.001
ALT	1.001 (0.999-1.002)	0.123		
Serum creatinine[1]	1.075 (1.013-1.197)	0.018		
Serum total bilirubin[1]	1.047 (1.012-1.083)	0.007		
Prothrombin time[1]	1.128 (1.043-1.221)	0.003		
Initial hepatic encephalopathy				
None	1		1	
Grade Ⅰ-Ⅱ	1.393 (0.558-3.477)	0.477	0.555 (0.200-1.537)	0.257
Grade Ⅲ-Ⅳ	2.229 (1.062-4.677)	0.034	0.969 (0.449-2.088)	0.935
Initial ascites				
None	1		1	
Mild	2.064 (1.003-4.250)	0.049	1.604 (0.766-3.361)	0.210
Moderate to severe	4.675 (2.494-8.766)	< 0.001	3.346 (1.715-6.527)	< 0.001
Glasgow-Blatchford score	0.980 (0.917-1.047)	0.550		
Rockall score	1.138 (0.968-1.338)	0.118		
Timing of endoscopy				
Non-urgent (≥ 12 h)	1			
Urgent (< 12 h)	1.297 (0.806-2.088)	0.284		

[1]Considering the multicollinearity between model for end-stage liver disease (MELD) score and its individual components, only MELD score, the most relevant prognostic parameter in cirrhosis, was included in the final multivariable model. HR: Hazard ratio; GI: Gastrointestinal; MELD: Model for end-stage liver disease; ALT: Alanine aminotransferase.

P = 0.004), high MELD score (aHR: 1.049; 95%CI: 1.024-1.074; *P* < 0.001), and the presence of ascites. In particular, the grade of ascites showed dose-dependency. When the ascites was present to a more than moderate degree, the 6-wk mortality was increased 3.346-fold compared to when there was no ascites. Also, the presence of HCC (aHR: 1.929; 95%CI: 1.072-3.469; *P* = 0.028) increased the risk of short-term mortality in variceal bleeding patients. However, the GBS and Rockall scores were not significantly associated with 6-wk mortality in patients with acute variceal bleeding. Similar results were obtained when the factors predicting transplantation or death were analyzed (Supplementary Table 1).

DISCUSSION
The decision as to when to perform endoscopy in patients with acute variceal bleeding has always been controversial. Guidelines have traditionally recommended that endoscopy be performed within 12 h of admission, but to date there has been little actual supporting evidence for this[4,5,16]. Our study analyzed relatively large

numbers of patients, and concluded that, despite the existing guidelines, the timing of endoscopy was not associated with short-term survival or mortality in patients with variceal bleeding.

Studies on the optimal timing of endoscopy in patients with acute variceal bleeding have taken place mostly at a time in the past when sclerotherapy was the mainstream treatment. Several randomized control trials reported at this time have concluded that, if endoscopy was performed early, clinical indices did not improve significantly[17,18]. In studies, including some meta-analyses, endoscopic treatment was recommended only when pharmacotherapy fails[19]. However, band ligation therapy has completely replaced sclerotherapy nowadays[20,21]. Moreover, it is now widely acknowledged that combination therapy is superior to pharmaco- or endoscopic monotherapy for acute variceal bleeding[22,23]. Paradoxically, however, in the age of band ligation, there has been little research so far on the optimal timing of endoscopy.

To date, there have been two relatively large-scale studies on the optimal timing of the endoscopy of variceal bleeding patients in the "band ligation era". In a

study published in Taiwan, early endoscopy (*i.e.*, < 15 h) reduced in-hospital mortality, but did not have a significant impact on mortality[9]. Another study published in Canada showed that time-to-endoscopy did not appear to be associated with mortality[8]. Both studies exhibited selection bias, in that only hemodynamically stable patients were included. The authors suggested that in-hospital mortality was increased due to delays in time-to-endoscopy, but the baseline MELD score was higher in those patients with higher in-hospital mortality (16.5 *vs* 11.2)[9]. In other words, it is difficult to tell whether these patients' increased in-hospital mortality was due to underlying liver disease or because of the delayed time-to-endoscopy. Finally, both studies analyzed the door-to-endoscopy time as a continuous variable, and therefore showed results that were not significant.

In our study, to overcome these limitations, we conducted IPW for baseline correction and analyzed "door-to-scope" time as a 12-h categorical variable according to the existing guidelines. Considering the degree to which the various factors that influence the timing of endoscopy may impact the clinical outcomes, it was essential to conduct the IPW. In fact, clinicians tend to perform endoscopy more quickly if the patient shows unstable features, and in this situation, the effect of endoscopy on survival is likely to be underestimated.

So, when is the appropriate time to do endoscopy in variceal bleeding? Research to date shows it is more complicated than just "the sooner the better". In the Taiwan study, the authors divided endoscopic timing into several stages, but they failed to prove "the sooner, the better" concept[9]. Although we have not described it in this study, we analyzed the results of a door-to-endoscopy time of 6 h, but we failed to demonstrate a benefit with more urgent endoscopy. It seems that timing of endoscopy and clinical outcomes, including mortality, shows a non-linear correlation. For example, in peptic ulcer bleeding patients, the correlation between the timing of endoscopy and clinical outcomes is *U*-shaped, and we consider it likely to be similar in variceal bleeding patients[24]. This phenomenon is believed to be due to the fact that basic resuscitation (*e.g.*, adequate hydration, antibiotics) influences the patient's outcome in the early stages of treatment[4,5,25]. If the patient is transported too early in order to undergo an endoscopic procedure, it may interfere with basic resuscitation during the critical early period of management, leading to a bad prognosis. Also, if the endoscopy is performed too soon, the quality of endoscopic examination may be suboptimal, due to poor preparation. In clinical practice, we sometimes find that delayed endoscopy, after using vasoactive drugs, is actually faster and safer.

In our study, the median door-to-endoscopy time in the non-urgent group was 19.5 h which was much longer than the recommended time. Although most guidelines recommend that endoscopy should be performed within 12 h of presentation, various clinical and facility factors may hamper guideline implementation in the real clinical settings[4,5,26,27]. To overcome these baseline

imbalances, we used IPW method. After IPW, there were no significant differences in the short-term outcomes between two groups.

When it comes to studies of endoscopy, it is important to consider the selection of appropriate outcomes. Previous studies have focused primarily on long-term prognosis, such as overall survival or all-cause mortality. These studies have failed to show a reduction in mortality in urgent endoscopy. However, since the long-term prognosis of patients with variceal bleeding is mainly related to their basal liver function, it is unreasonable to associate a single-point endoscopy with a long-term prognosis. Indeed, in our data and in the Canadian studies, the most common cause of death was liver cirrhosis, not the bleeding itself (Supplementary Table 2). For this reason, unlike other studies, in our study we changed the endpoint to overall survival at 6 wk or TFS at 6 ws. We consider short-term outcomes to be more appropriate than long-term outcomes in demonstrating the precise effect of endoscopic timing on prognosis. In fact, the Barveno guideline recommends 6-wk mortality rather than OS as an outcome[5].

Consistent with previous reports, the length of hospital stay was statistically different between the urgent group and non-urgent group[10,28-30]. It may be due to more accurate diagnosis and earlier hemostasis of the bleeding source by urgent endoscopy, leading to decrease in the subsequent resource use including the length of stay and total hospitalization costs.

There are some limitations to our study. First, as with other studies, our study may be confounded by unmeasured factors because of its retrospective design. Clearly there are ethical difficulties in enrolling acute variceal bleeding patients into RCTs; nevertheless retrospective studies can be of benefit in providing reliable and practical information. Second, where there is no weekend rounder, the results of this study may be difficult to apply. Another issue to consider is that previous research refers to geographic variability in prognosis of UGIB patients.

In conclusion, we demonstrated that endoscopic timing may not affect the clinical outcomes of patients with esophageal variceal bleeding, especially in short-term outcomes. Therefore it is necessary to perform endoscopy at an appropriate time, depending on each patient's condition. A prospective study, or a meta-analysis involving a greater number of centers in different countries, will assist in establishing a more accurate optimal timing for endoscopy.

ARTICLE HIGHLIGHTS

Research background
The optimal timing of emergency endoscopy in acute variceal bleeding remains unclear. Most guidelines recommend performing endoscopy for acute variceal bleeding within 12 h of admission. However, the evidence level for this recommendation is very low, with few relevant studies to date to justify it

Research motivation
Determining the appropriate endoscopic timing is a very important issue, and

both the risk and benefit to the patient need to be considered. We hypothesized that the earlier the endoscopy was performed, the better the short-term prognosis of the cirrhotic patients with variceal bleeding.

Research objectives

The aim of this study was to examine the association between the timing of endoscopy and the short-term prognosis of acute variceal bleeding in cirrhotic patients.

Research methods

We performed a retrospective study of cirrhotic patients with variceal bleeding. Patients were divided into two groups according to the time of endoscopy. Urgent endoscopy group was defined as performing endoscopy before 12 h of admission and non-urgent endoscopy group after 12 h of admission. The inverse probability weighting (IPW) method based on propensity score was applied to correct baseline differences between the two groups, and compared short-term prognosis between the two groups.

Research results

In 274 patients, 173 patients received urgent endoscopy, and 101 patients received non-urgent endoscopy. After IPW method, short term prognosis including 6-wk mortality rate or 6-wk transplantation rate was not different between the two groups. In multivariate analyses, timing of endoscopy was not associated with 6-wk mortality. Other factors associated with 6-wk mortality were age, hepatocellular carcinoma, MELD score, and degree of ascites.

Research conclusions

Timing of endoscopy may not affect the clinical short-term outcomes of patients with esophageal variceal bleeding.

Research perspectives

Because this is a retrospective study, a prospective study to determine the appropriate timing of endoscopy considering risk and benefit is needed for the future.

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