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Optimal endoscopy timing according to the severity of underlying liver disease in patients with acute variceal bleeding

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ABSTRACT

Background: Current guidelines recommend endoscopic therapy to be performed within 12 h for acute variceal bleeding (AVB). However, the optimal timing of endoscopic therapy for AVB remains unclear.
Aims: To examine the relationship between the endoscopy timing and clinical outcomes in AVB, with emphasis on liver function and endoscopy timing.
Methods: From January 2010 to June 2017, cirrhotic patients with AVB confirmed by endoscopy were evaluated. The primary outcome was a composite of 6-week rebleeding and mortality. We stratified patients according to the MELD score.
Results: In 411 patients, the overall composite outcome rate was 30.9% (n = 127) at 6 week. Patients who underwent urgent endoscopy (≤12 h) had a significantly higher composite outcome than patients who underwent non-urgent endoscopy (>12 h) (34.4% vs. 19.1%; P = 0.005). Low-risk patients who underwent urgent endoscopy were more likely to reach the composite outcome (adjusted OR, 0.84 per 4 h; 95% CI, 0.73–0.98; P = 0.027). These findings persisted even after adjustment for baseline characteristics between the urgent and non-urgent groups.
Conclusions: Urgent endoscopy is significantly associated with a poorer outcome in patients with AVB, especially in low-risk patients. Our result provides a treatment strategy according to the severity of underlying liver disease in patients with AVB.

1. Introduction

Acute variceal bleeding (AVB) is a life-threatening complication of liver cirrhosis associated with mortality rates of 20–25% [1,2]. Endoscopic band ligation (EBL) combined with terlipressin is currently the treatment of choice for the management of AVB [3]. Current guidelines recommend endoscopic therapy to be performed within 12 h for AVB [3,4]. However, these recommendations are based on expert opinions and not on clinical trials or large observational studies.

A previous study revealed that endoscopy timing was not related to mortality in hemodynamically stable AVB patients [5]. However, another study found delayed endoscopy to be an independent risk factor for mortality in AVB patients [6]. A recent study reported hematemesis as an indicator for urgent endoscopy, while the endoscopy timing was not important in patients without hematemesis [7]. This lack of consistency among studies raises questions regarding the optimal timing of endoscopy in AVB patients. The existing data suggest that some patients would benefit from early endoscopy, while endoscopy may be delayed in others.

Several factors, including the advanced Child-Turcotte-Pugh (CTP) score, model for end-stage liver disease (MELD) score, bacterial infection, hepatic venous pressure gradient (HVPG), hepatocellular carcinoma, hypovolemic shock, old age, and alcoholic etiology, have been identified to predict outcome in AVB patients [2,8–11]. While the severity of the underlying liver disease is a main predictor of outcome in patients with AVB, previous studies have not stratified patients according to their liver function. Thus, it is unclear whether the effect of urgent endoscopy is modified according to the severity of liver dysfunction [5–7].

The aim of this study was to examine the relationship between the endoscopy timing and clinical outcome in patients with AVB. In

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addition, we aimed to investigate whether the timing of endoscopy would have different effect according to the severity of liver dysfunction.

2. Materials and methods

2.1. Study population

Medical records from Incheon St. Mary's Hospital, The Catholic University of Korea were retrospectively reviewed between January 2010 and June 2017. Patients were enrolled if they satisfied the following criteria: (1) age >18 years; and (2) esophageal or gastric varices confirmed as the source of bleeding. The exclusion criteria were as follows: (1) severe dysfunction of a major organ (e.g., heart failure, pulmonary disease, and terminal malignancy except hepatocellular carcinoma); (2) history of EBL or sclerotherapy within three months; and (3) loss to follow-up within three months after AVB. The Institutional Review Boards (IRBs) of the Catholic University College of Medicine approved this study. (approval number: 2018-0231-0001).

2.2. Data collection

Two independent investigators (C.W.H., J.S.K.) reviewed the medical records, including demographic, laboratory, clinical and endoscopic data. The Charlson comorbidity index, CTP score and MELD score were calculated from the data.

2.3. Endoscopic procedure

When patients with suspected AVB presented to the hospital, terlipressin was administered for 24–72 h along with intravenous ceftriaxone at 1–2 g/24 h for 5–7 days [3]. The timing of endoscopy depended on the discretion of the endoscopists on duty, the patient's will and hemodynamic status. Therapeutic endoscopy was performed using a standard video endoscope (GIF-Q260 or GIF-HQ290; Olympus, Tokyo, Japan). We performed EBL with endoscopic ligating devices (Sumitomo Bakelite, Tokyo, Japan) and sclerotherapy by injecting 0.5 mL of *N*-butyl-cyanoacrylate (Histoacryl; Braun, Rubi, Spain) mixed 1:1 with 0.5 mL of lipiodol (Guerbet, Aulnay-sous-Bois, France). Esophageal varices and type 1 gastroesophageal varices (GOV 1) were treated with EBL, and type 2 gastroesophageal varices (GOV 2) and isolated gastric varices (IGV 1 and 2) were treated with sclerotherapy [12]. Endoscopic therapy was performed based on the observation of one of the following: (a) active bleeding from varices (blood spurting or oozing from the varices); (b) the "white nipple" sign or an adherent blood clot; (c) blood in the upper gastrointestinal tract with varices as the only potential bleeding source; and (d) the presence of varices without blood in the upper gastrointestinal tract. In the case of (d), EBL or sclerotherapy was performed depending on the discretion of the on-duty endoscopists.

2.4. Definitions

The timing of endoscopy was defined as the interval between the patient's arrival at the emergency department and the endoscopic examination procedure start time. In patients with in-hospital bleeding, the time to endoscopy was defined as the time interval from the development of symptoms to the procedure start time. Endoscopy performed in ≤12 h was considered urgent endoscopy, and endoscopy performed in >12 h was considered non-urgent endoscopy. The severity of gastroesophageal varices was graded according to the classification by the Japanese Research Society for Portal Hypertension [13]. Infection was defined using standard guidelines [14]. Rebleeding was defined as hematemesis, melena or hematochezia with accompanying laboratory (hemoglobin drop of greater than 2 g/dL within 24 h) or vital sign changes (systolic blood pressure decrease to <100 mmHg or heart rate increase to >100 beats/min). Mortality was defined as in-hospital mortality.

2.5. Outcome assessment

The primary composite outcome was 6-week rebleeding and mortality. The secondary outcomes were the successful endoscopic hemostasis, the need for salvage therapy (e.g., balloon tamponade, additional endoscopic therapy, transjugular intrahepatic portosystemic shunt [TIPS]), the length of hospital stay, the total number of blood units transfused, and the number of endoscopies performed during hospitalization.

2.6. Statistical analysis

The chi-square test and Fisher's exact test were used to evaluate associations among various categorical variables, and the *t*-test was used for continuous variables in the intergroup comparisons of clinical characteristics. The Youden method was used to identify an optimal cut off level in the receiver operating characteristic (ROC) curve to maximize the sensitivity and specificity. Propensity score matching was used for 1:1 matching to adjust the difference between the urgent and non-urgent groups. Propensity scores included the following variables: age, sex, Charlson comorbidity index, hematemesis, hepatocellular carcinoma, infection, etiology of liver disease, type of varices, systolic blood pressure, heart rate, laboratory findings, CTP score, and MELD score. The Kaplan–Meier method was used to determine the cumulative 6-week composite outcome rates after AVB, and comparisons were made by the log-rank test. The accepted significance level was a $P < 0.05$. All statistical analyses were performed using SPSS version 20.0 for Windows (SPSS Inc., Chicago, IL, USA), SAS version 9.2 (SAS Institute, Cary, NC, USA) and MedCalc version 12.7.0 (MedCalc Software, Ostend, Belgium).

3. Results

3.1. Patient characteristics

Overall, 505 patients were admitted due to AVB between January 2010 and June 2017 at our institution. Among them, 94 patients were excluded according to the exclusion criteria (severe dysfunction of a major organ, n = 10; history of EBL or sclerotherapy within three months, n = 62; lost to follow-up within three months following variceal bleeding, n = 22). The remaining 411 patients were included in this analysis. The average time to endoscopy was 11.2 h. The average CTP and MELD score was 8.3 and 12.1, respectively. Three hundred seventeen patients (77.1%) underwent urgent endoscopy, and 94 patients (22.9%) underwent non-urgent endoscopy (Table 1). The baseline patient characteristics, including CTP and MELD scores, did not differ between the two groups. However, patients who underwent urgent endoscopy were more likely to have a higher heart rate (98.4 vs. 88.7; $P = 0.007$). The median time to endoscopy was significantly different between the two groups (4.9 h vs. 32.7 h; $P < 0.001$).

3.2. Clinical outcomes according to endoscopy timing

The overall composite outcome rate was 30.9% (n = 127). The overall rebleeding rate was 28.0% (n = 115), and the overall mortality rate was 11.4% (n = 47) at 6 weeks. Patients who underwent urgent endoscopy (≤12 h) had a significantly higher composite outcome than patients who underwent non-urgent endoscopy (>12 h)

Table 1
Characteristics of patients receiving urgent (≤12 h) versus non-urgent (>12 h) endoscopy.

Characteristics	Overall (n = 411)	Urgent endoscopy (n = 317)	Non-urgent endoscopy (n = 94)	P
Age (years)	53.6 ± 11.3	53.9 ± 11.6	52.6 ± 10.6	0.300
Sex (male)	291 (70.8%)	226 (71.3%)	65 (69.1%)	0.688
In-hospital bleeding	30 (7.2%)	22 (6.9%)	8 (8.5%)	0.607
Charlson comorbidity index	4.0 ± 1.1	4.0 ± 1.1	4.0 ± 0.9	0.809
Hematemesis	296 (72.0%)	232 (73.7%)	64 (71.9%)	0.743
HCC	104 (25.3%)	80 (25.3%)	24 (25.5%)	0.966
Etiology of liver disease				0.278
Alcohol	240 (58.4%)	181 (57.8%)	59 (62.8%)	
HBV	108 (26.3%)	86 (27.5%)	22 (23.4%)	
HCV	28 (6.8%)	19 (6.1%)	9 (9.6%)	
Other	31 (7.5%)	27 (8.6%)	4 (4.3%)	
Gastric varices	72 (17.5%)	57 (18.0%)	15 (16.0%)	0.521
Infection	63 (15.3%)	54 (17.0%)	9 (9.6%)	0.078
Systolic blood pressure (mmHg)	107.0 ± 24.8	107.3 ± 25.6	106.2 ± 22.1	0.712
Heart rate (beat/min)	96.2 ± 20.8	98.4 ± 21.0	88.7 ± 18.5	<0.001
Hematocrit (%)	25.7 ± 6.9	25.8 ± 7.1	25.4 ± 6.3	0.611
Platelet (10^3/mm^3)	102.3 ± 60.9	103.1 ± 62.5	99.5 ± 55.9	0.612
BUN (mg/dl)	29.0 ± 17.2	29.6 ± 17.7	27.0 ± 15.5	0.203
CTP score	8.3 ± 2.4	8.2 ± 2.4	8.5 ± 2.4	0.222
MELD score	12.1 ± 6.9	12.3 ± 7.1	11.5 ± 6.4	0.326
Timing to endoscopy (hours)	11.2 ± 23.1	4.9 ± 3.0	32.7 ± 41.7	<0.001

HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; BUN, blood urea nitrogen; CTP, Child-Turcotte-Pugh; MELD, model for end-stage liver disease.

Table 2
Outcome in patients receiving urgent (≤12 h) versus non-urgent (>12 h) endoscopy.

Outcome	Overall (n = 411)	Urgent endoscopy (n = 317)	Non-urgent endoscopy (n = 94)	P
Primary outcome				
Composite outcome	127 (30.9%)	109 (34.4%)	18 (19.1%)	0.005
Components of primary outcome				
Re-bleeding	115 (30.0%)	98 (30.9%)	17 (18.1%)	0.015
Death	47 (11.4%)	40 (12.6%)	7 (7.4%)	0.166
Secondary outcomes				
Successful hemostasis	302 (84.6%)	229 (83.0%)	73 (90.1%)	0.117
Need for salvage therapy	55 (13.4%)	47 (14.8%)	8 (8.5%)	0.114
Number of units transfused	4.1 ± 3.8	4.4 ± 4.0	3.1 ± 2.7	0.004
Number of endoscopy	1.5 ± 0.7	1.6 ± .7	1.2 ± 5.2	<0.001
Length of stay	11.9 ± 9.8	11.9 ± 10.6	11.8 ± 6.4	0.892

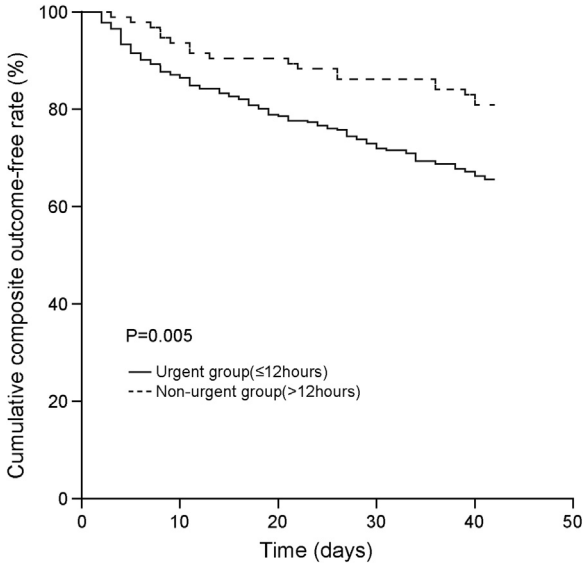

Fig. 1. Kaplan–Meier estimates of 6-week composite outcome in patients with acute variceal bleeding stratified by the endoscopy timing.

(34.4% vs. 19.1%; P = 0.005) (Fig. 1). The number of transfusions per patient (4.4 vs. 3.1; P = 0.004) and the number of endoscopies performed during hospitalization (1.6 vs. 1.2; P < 0.001) were also significantly higher in the urgent than in the non-urgent group. However, the length of hospital stay was not different between the two groups (Table 2).

3.3. Predictive factors of 6-week composite outcome

By multivariate analysis, time to endoscopy was a significant predictor of the composite outcome (adjusted OR, 0.94; 95% CI, 0.89–0.99; P = 0.036), with a 6% reduced risk of reaching the composite outcome with increased time to endoscopy (per 4-h interval). Other significant predictors were older age (adjusted OR, 1.27 per 10 years; 95% CI, 1.02–1.58; P = 0.034), infection (adjusted OR, 15.79; 95% CI, 7.38–33.79; P < 0.001), low systolic blood pressure (adjusted OR, 0.89 per 10 mmHg; 95% CI, 0.80–0.99; P = 0.039), higher MELD score (adjusted OR, 1.08; 95% CI, 1.03–1.12; P < 0.001), and observation without endoscopic therapy (adjusted OR, 7.46; 95% CI, 3.94–14.16; P < 0.001) (Table 3).

3.4. Risk stratification by MELD score

Multivariate analysis revealed that the MELD score was a significant predictor of the composite outcome. Therefore, by plotting the ROC curve of the MELD score for the primary composite outcome (6-week rebleeding or mortality), we determined 17 points as the optimal cut off value for predicting the composite outcome. The area under the ROC curve was 0.610 (95% CI, 0.547–0.672) (Supplementary Fig. 1). Based on this score, we divided the patients into two groups: low-risk patients (MELD score ≤17) and high-risk patients (MELD score >17).

Table 3
Univariate and multivariate analysis of predictors of composite outcome.

Predictor	Univariate OR	P	Mutivariate OR	P
Time to endoscopy (per 4 h)	0.96 (0.97–1.01)	0.184	0.94 (0.89–0.99)	0.036
Clinical characteristics				
Age (per 10 years)	1.18 (0.98–1.42)	0.080	1.27 (1.02–1.58)	0.034
Sex (male)	1.26 (0.79–2.01)	0.339	–	
Charlson comorbidity index	1.31 (1.07–1.59)	0.008	–	
Hematemesis	1.03 (0.64–1.65)	0.919	–	
HCC	1.57 (0.99–2.51)	0.061	–	
Etiology of liver disease (alcohol)	1.36 (0.88–2.09)	0.170	–	
Infection	13.54(6.99–26.21)	<0.001	15.79 (7.38–33.79)	<0.001
Vital signs				
Systolic blood pressure (per 10 mmHg)	0.92 (0.84–0.99)	0.044	0.89 (0.80–0.99)	0.039
Heart rate (beat/min)	1.00 (0.99–1.01)	0.317	–	
Prognostic scores				
CTP score	1.27 (1.16–1.39)	<0.001	–	
MELD	1.08 (1.05–1.11)	<0.001	1.08 (1.03–1.12)	<0.001
Endoscopic findings				
Varix size (F3)	1.36 (0.89–2.01)	0.161	–	
Gastric variceal bleeding	1.24 (0.72–2.11)	0.440	–	
Spurting/oozing	1.18 (0.71–1.96)	0.525	–	
Observation without therapy	2.99 (1.81–4.95)	<0.001	7.46 (3.94–14.16)	<0.001

HCC, hepatocellular carcinoma; CTP, Child-Turcotte-Pugh; MELD, model for end-stage liver disease.

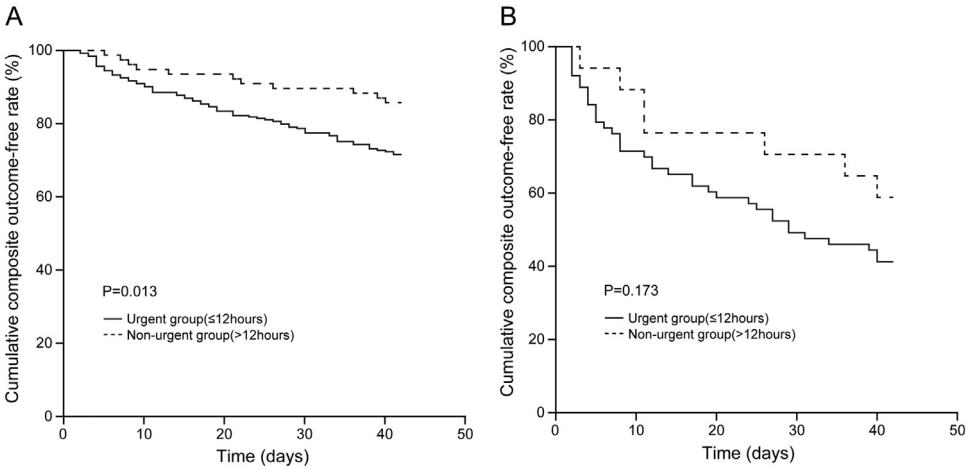

Fig. 2. Kaplan–Meier estimates of 6-week composite outcome in patients with acute variceal bleeding stratified by the severity of the underlying liver disease and the endoscopy timing.
(A) Low-risk patients, (B) high-risk patients.

3.5. Endoscopy timing in low-risk patients (MELD score ≤17)

There were 331 low-risk patients (80.5%), of whom 83 patients (25.1%) reached the primary composite outcome. The overall rebleeding rate was 24.5% (n = 81), and the overall mortality rate was 4.8% (n = 16). In low-risk patients, urgent endoscopy (≤12 h) resulted in a significantly higher composite outcome (28.3% vs. 14.3%; P = 0.013) than non-urgent endoscopy (>12 h) (Fig. 2A). Multivariate analysis revealed time to endoscopy as a significant predictor for composite outcome in low-risk patients (adjusted OR, 0.84 per 4 h; 95% CI, 0.73–0.98; P = 0.027). Increased time to endoscopy resulted in reduced odds of reaching the composite outcome. Other significant predictors of composite outcome were infection and observation without endoscopic therapy (Table 4).

3.6. Endoscopy timing in high-risk patients (MELD score >17)

There were 80 high-risk patients (19.5%), of whom 44 patients (55.0%) reached the primary composite outcome. The overall rebleeding rate was 42.5% (n = 34), and the overall mortality rate was 38.8% (n = 31). There was no significant difference in the composite outcome in high-risk patients who underwent urgent versus non-urgent endoscopy (Fig. 2B). Multivariate analysis showed that time to endoscopy was also not a significant predictor of composite outcome in high-risk patients (adjusted OR, 0.99 per 4 h; 95% CI, 0.93–1.05; P = 0.692). The only significant predictor for the composite outcome in high-risk patients was infection (adjusted OR, 13.66; 95% CI, 4.06–45.89; P < 0.001) (Table 4).

Table 4
Multivariate analysis of predictors of composite outcome stratified by the severity of the underlying liver disease.

Predictor	Mutivariate OR	P
MELD score (≤17) — low risk (n = 331)		
Time to endoscopy (per 4 h)	0.84 (0.73–0.98)	0.027
Infection	10.59 (4.46–25.20)	<0.001
Observation without therapy	4.66 (2.50–8.68)	<0.001
MELD score (>17) — high risk (n = 80)		
Time to endoscopy (per 4 h)	0.99 (0.93–1.05)	0.692
Infection	13.66 (4.06–45.89)	<0.001
Observation without therapy	2.94 (0.35–25.00)	0.323

MELD, model for end-stage liver disease.

3.7. Endoscopy timing after 1:1 propensity score matching between urgent and non-urgent groups

After adjustment for heart rate and 1:1 matching between the urgent and non-urgent groups (urgent group, n = 73; non-urgent group, n = 73) (Supplementary Table 1), urgent endoscopy (≤12 h) was also a significant predictor of the composite outcome (adjusted OR, 5.81; 95% CI, 1.87–18.18; P = 0.002) (Supplementary Table 2). Urgent endoscopy resulted in a significantly higher composite outcome than non-urgent endoscopy in low-risk patients (adjusted OR, 7.63; 95% CI, 1.95–30.30; P = .003). Unlike low-risk patients, the endoscopy timing was not a significant predictor in the high-risk patients (adjusted OR, 2.57; 95% CI, 0.35–18.86; P = 0.353) (Supplementary Table 3).

4. Discussion

To the best of our knowledge, three studies have investigated the optimal timing of endoscopic treatment in AVB patients. However, these studies did not stratify patients according to the severity of their liver disease [5–7]. Therefore, we performed our study to evaluate the relationship between the endoscopy timing and clinical outcome in AVB patients stratified by severity of liver dysfunction.

We found that the endoscopy timing was a significant predictor of the composite outcome, including 6-week rebleeding and mortality. Patients who underwent urgent endoscopy (≤12 h) had a significantly higher composite outcome than patients who underwent non-urgent endoscopy (> 12 h). In the subgroup analysis, urgent endoscopy remained a significant predictor of the composite outcome in low-risk patients (MELD score ≤17).

Although experts suggest performing endoscopy as soon as possible for AVB, the optimal timing of endoscopic therapy for AVB remains controversial. A retrospective study of 210 patients with hemodynamically stable AVB showed no significant association between time to endoscopy and mortality [5]. In contrast, a larger retrospective study of 311 patients compared early endoscopy (≤15 h) with delayed endoscopy (> 15 h) and demonstrated that delayed endoscopy was an independent risk factor for in-hospital mortality in AVB [6]. Similarly, a recent retrospective study revealed that early endoscopy (≤12 h) was associated with a better outcome in patients presenting with hematemesis. However, there was no apparent association between the endoscopy timing and mortality or rebleeding in patients without hematemesis [7].

The results of our study suggest that low-risk patients (MELD score ≤17) may not benefit from urgent endoscopy in terms of 6-week rebleeding and mortality. There are some possible explanations for this result. First, the quality of the endoscopic examination and therapy may be inadequate in 'urgent' endoscopy due to remaining food and blood in the stomach. Second, urgent endoscopy may be associated with suboptimal resuscitation. Sufficient time for pre-endoscopic optimization of the patient's clinical state may be more determinant rather than the timing of endoscopy in low-risk patients. Although caution should be exercised when interpreting these results, the current recommendation of performing endoscopy within 12 h may not be optimal for all patients with AVB, especially low-risk patients.

The MELD score is a well-known prognostic score that can be easily calculated at initial presentation in cirrhosis patients [8,9,15]. Several studies have shown a strong correlation between the MELD score and prognosis of cirrhosis patients with AVB [8,9,16]. Reverter et al. showed that MELD values ≥19 predicted at least 20% mortality among patients with AVB [8]. Thus, the clinical outcome of cirrhosis patients with AVB is closely associated with the MELD score. To our knowledge, no studies have investigated the optimal timing of endoscopy according to the severity of the underlying liver disease. Our study is the first to assess whether patients with a low or high risk based on liver function have different outcomes with different times to endoscopy.

The results of our study show that the severity of the underlying liver disease can predict prognosis and could therefore help to classify patients into different risk strata, opening the possibility of individualizing treatment strategies for patients with AVB. Regarding low-risk patients, it may be more beneficial to delay the endoscopic intervention until the administration of adequate medical management (e.g., intravenous terlipressin, antibiotics, and fluid resuscitation). In high-risk patients, early prophylactic antibiotics and proper infection management may be more important than the endoscopy timing. Moreover, early TIPS within 72 h after initial pharmacological and endoscopic therapy should be considered in high-risk patients [3,17].

Our study has some limitations. The major limitation of this study is that patients who underwent urgent endoscopy were sicker with faster baseline heart rates. The timing of endoscopy was also subjective due to the retrospective nature of this study. Although we tried to adjust for this by performing propensity score matching, we may not have accounted for all potential confounders. Patient randomization would be the best way to address this limitation but would be difficult due to obvious ethical issues. Second, we did not evaluate otherimportant clinical factors associated with AVB, such as the HVPG. Previous studies have reported an HVPG >20 mmHg as an important predictor of adverse outcomes in AVB [18,19]. However, measuring the HVPG in emergency situations is very difficult. On the other hand, the MELD score can be calculated easily and quickly even in emergency situations. Several studies have demonstrated a strong correlation between the MELD score and the HVPG [20,21]. Despite these limitations, this is the first study to establish risk factors, including endoscopy timing, for poorer outcome in AVB by the liver disease severity.

In conclusion, in patients with AVB, the endoscopy timing is a significant indicator of 6-week rebleeding and mortality. Urgent endoscopy (≤12 h) is significantly associated with a poorer outcome in low-risk patients, whereas endoscopy timing is not associated with outcome in high-risk patients. Although additional prospective studies are needed to validate our results, this study provides a treatment strategy according to the severity of the underlying liver disease in patients with AVB.

Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.dld.2019.01.013.

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