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Timing of endoscopy for acute variceal bleeding in patients with cirrhosis (CHESS1905): A nationwide cohort study

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Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AVB, acute variceal bleeding; ICU, intensive care unit; IQR, interquartile range; PSM, propensity score matching; SBP, systolic blood pressure.

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Abstract

Background: Endoscopy plays an important role in the management of acute variceal bleeding (AVB) in patients with cirrhosis. This study aimed at determining the optimal endoscopy timing for cirrhotic AVB.

Methods: Patients with cirrhosis with AVB across 34 university hospitals in 30 cities from February 2013 to May 2020 who underwent endoscopy within 24 hours were included in this study. Patients were divided into an urgent endoscopy group (endoscopy <6 h after admission) and an early endoscopy group (endoscopy 6–24 h after admission). Multivariable analysis was performed to identify risk factors for treatment failure. Primary outcome was the incidence of 5-day treatment failure. Secondary outcomes included in-hospital mortality, need for intensive care unit, and length of hospital stay. A propensity score matching analysis was performed. In addition, we performed an analysis, in which we compared the 5-day treatment failure incidence and the in-hospital mortality among patients with endoscopy performed at <12 hours and 12–24 hours.

Results: A total of 3319 patients were enrolled: 2383 in the urgent endoscopy group and 936 in the early endoscopy group. After propensity score matching, on multivariable analysis, Child-Pugh class was identified as an independent risk factor for 5-day treatment failure (HR, 1.61; 95% CI: 1.09–2.37). The incidence of 5-day treatment failure was 3.0% in the urgent endoscopy group and 2.9% in the early group ($p = 0.90$). The in-hospital mortality was 1.9% in the urgent endoscopy group and 1.2% in the early endoscopy group ($p = 0.26$). The incidence of need for intensive care unit was 18.2% in the urgent endoscopy group and 21.4% in the early endoscopy group ($p = 0.11$). The mean length of hospital stay was 17.9 days in the urgent endoscopy group and 12.9 days in the early endoscopy group ($p < 0.05$). The incidence of 5-day treatment failure in the <12-hour group was 2.3% and 2.2% in the 12–24 hours group ($p = 0.85$). The in-hospital mortality was 2.2% in the <12-hour group and 0.5% in the 12–24 hours group ($p < 0.05$).

Conclusions: The data suggest that performance of endoscopy within 6–12 or within 24 hours of presentation among patients with cirrhosis with AVB led to similar treatment failure outcomes.

INTRODUCTION

Acute variceal bleeding (AVB) is one of the most common and severe complications in liver cirrhosis and portal hypertension.[1–3] Despite advances in management and therapy, mortality 6 weeks after AVB remains up to 20%.[4,5] Currently, emergency resuscitation, intravenous somatostatin analogs or vasoconstrictors, antibiotics, and endoscopic therapy are important initial management strategies in AVB.[3] The American College of Gastroenterology recommends emergency endoscopy within 24 hours after the presentation for patients with acute upper gastrointestinal bleeding, and an international consensus group suggests that emergency endoscopy allows timely diagnosis as well as treatment of bleeding, which reduces the risk of early rebleeding and death and the need for operation.[6,7] However, the optimal timing of emergency endoscopic treatment for patients with AVB is empirical. Although recent practice guidelines have recommended emergency endoscopy within 12 hours for all patients suspected of having

AVB,[2,3] these recommendations are based on expert opinions and not on large observational and multicenter studies.

Results from prior retrospective studies without statistical adjustment have been mixed and heterogeneous.[8,9] A recent meta-analysis suggested benefits in overall mortality with earlier versus delayed endoscopy but did not reveal benefits in rebleeding or mortality with endoscopy performed within 12 hours versus beyond 12 hours in patients with cirrhosis with AVB.[10] In addition, a recent study also reported that optimal endoscopy timing varied according to the severity of underlying liver disease in patients with AVB.[11] Urgent endoscopy may allow earlier identification of bleeding, as well as better control of bleeding and risk stratification, and possibility of prevention of rebleeding.[12] However, endoscopy-related complications may limit these benefits.[13,14] This lack of consistency among studies raises questions regarding the optimal timing of emergency endoscopy in patients with AVB.

Multiple prognostic indicators have been identified to predict mortality after AVB,[5,15–17] although these outcome predictors lack stratification.[8–11] A recent randomized controlled trial demonstrated noninferiority of early endoscopy when compared with urgent endoscopy in acute gastrointestinal bleeding but was unable to draw conclusions specifically for AVB due to the small number of recruited patients (8.5%).[18]

The aim of this study was to assess the optimal emergency endoscopic intervention timing for AVB based on large-scale data from multiple centers and to assess and compare the rate of early treatment failure, in-hospital mortality, need for intensive care unit (ICU), and length of hospital stay in patients undergoing urgent endoscopy (timing of endoscopy <6 h after admission) and early endoscopy (timing of endoscopy 6–24 h after admission) for AVB.

METHODS

Study design and patients

Complete demographic and clinical data of patients with cirrhosis associated with AVB who underwent emergency endoscopy within 24 hours between February 2013 and May 2020 across 34 university hospitals from 30 cities in China were retrospectively reviewed (ClincialTrials.gov number, NCT04957875). Two independent investigators (Chuan Liu and Yifei Huang) reviewed the medical records, including demographic, laboratory, clinical, and endoscopic data. Inclusion criteria were as follows: (1) age 18 years or older; (2) established diagnosis of cirrhosis (based on liver biopsy or the combination of clinical, biochemical, and imaging findings); (3) witnessed or reported evidence of gastrointestinal hemorrhage (hematemesis, melenemesis, or hematochezia); and (4) esophageal or gastric varices confirmed endoscopically as the source of bleeding. Exclusion criteria were as follows: (1) severe dysfunction of a major extrahepatic organ (eg, heart failure, pulmonary disease, and terminal malignancy except hepatocellular carcinoma); (2) history of endoscopic therapy for varices (ligation or sclerotherapy) within 3 months; and (3) incomplete or missing data. The study was performed in accordance with the ethical guidelines of the Declaration of Helsinki and was approved by the Institutional Review Board. The informed consent was waived for the retrospective analysis.

Management of acute variceal bleeding

When patients with cirrhosis presented with AVB to the emergency department, emergency physicians consulted gastroenterologists on duty to assess the patient for suitability for endoscopy, usually after initial stabilization. Performance of endoscopy and its timing was at the discretion of the gastroenterologist on call. Therapeutic endoscopy for AVB was performed within 24 hours after consultation by an experienced attending endoscopist, using standard forward-viewing upper gastrointestinal video endoscopes at individual centers. Written informed consent for endoscopy was obtained before each procedure. The standard of care at all hospitals was to administer a vasoactive agent and antibiotics upon the patient's presentation. Packed red blood cells were transfused at the discretion of the attending gastroenterologist.

Outcomes

The primary outcome was the incidence of 5-day treatment failure after emergency endoscopy, which was defined by either absence of control of bleeding or rebleeding within the first 5 days. The secondary outcomes included in-hospital mortality, need for ICU, and length of hospital stay. The timing of emergency endoscopy was defined as the interval between the patient's arrival at the emergency department and the endoscopic examination procedure start time. Endoscopy performed in <6 hours was considered urgent endoscopy, and endoscopy performed in 6–24 hours was considered early endoscopy. Rebleeding was defined as new-onset hematemesis, coffee ground emesis, melena, or hematochezia with accompanying laboratory abnormality consistent with bleeding (specifically, a drop in Hb of >2 g/dL within 24 h) or vital sign changes [systolic blood pressure (SBP) decreasing to <90 mm Hg or heart rate increasing to >100 beats/min].

Propensity score matching

Propensity score matching (PSM) was used for 1:1 matching to achieve a balance at baseline (ie, minimal confounding) between the urgent and early groups. Final covariates included the following variables: age, sex, SBP, heart rate, bleeding history, Child-Pugh class, and the laboratory tests. Patients in the urgent endoscopy group were matched to the early endoscopy group using the closest estimated propensity score within 0.1 of the SD of the logit of PSM, using a matching ratio of 1:1.

The 5-day treatment failure incidence and the in-hospital mortality in patients with endoscopy performed <12 hours and 12–24 hours

We performed an additional analysis, in which we compared the 5-day treatment failure incidence and the in-hospital mortality among patients with endoscopy performed <12 hours and 12–24 hours because the current guidelines recommend to perform upper endoscopy within 12 hours[2,3]

Statistical analyses

We determined that a sample of 330 patients per group would provide 90% power to detect a 6%-point difference (12% vs 6%) in 5-day treatment failure, with a 2-sided α level of 5%.

Continuous variables were reported as median with interquartile range and were compared using the Mann-Whitney test. Variables with normal distributions were reported as mean and SD and were compared using the Student *t* tests. Categorical data, presented as frequencies (%), were compared using the chi-square test or the Fisher exact test. The cumulative probability curves were generated using the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate analyses were assessed using a Cox proportional hazards stepwise model. Factors with a $p < 0.05$ on univariate analysis were incorporated into multivariate analysis. After PSM, univariate, multivariate logistic regression, and Kaplan-Meier analyses were also performed. The data analyses were performed using the *R* language (Version 4.0.3, R Core Team, 2020). A $p < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

A total of 3319 patients across 34 university hospitals from 30 cities in China (Supplemental Figure S1, http://links.lww.com/HC9/A275) were included. There were 2383 patients in the urgent endoscopy group and 936 patients in the early endoscopy group. Hepatitis *B*, alcohol, and hepatitis *C* were the most 3 common etiologies of cirrhosis in 1167 (49%), 217 (9%), and 164 (7%) patients in the urgent endoscopy group, respectively, and 469 (50%), 160 (17%), and 64 (7%) patients in the early endoscopy group, respectively. The groups were similar in terms of sex, presentation SBP, heart rate, and laboratory tests (Table 1). After PSM, 935 patients were analyzed in each

TABLE 1 Baseline characteristics

	Overall (n = 3319); n (%)	Urgent endoscopy group (n = 2383); n (%)	Early endoscopy group (n = 936); n (%)
Age (y), mean (SD)	54.33 (11.41)	54.04 (11.40)	55.07 (11.42)
Sex (M)	2356 (70.99)	1699 (71.3)	657 (70.3)
SBP, mean (SD)	114.32 (17.60)	114.35 (17.53)	114.24 (17.81)
Heart rate, mean (SD)	86.47 (22.00)	86.35 (23.64)	86.82 (17.15)
With a bleeding history	2086 (62.85)	1590 (66.7)	496 (53.00)
Child-Pugh			
Class *A*	857 (25.82)	532 (22.3)	325 (34.7)
Class *B*	1844 (55.56)	1366 (57.3)	478 (51.1)
Class *C*	618 (18.62)	485 (20.4)	133 (14.2)
Laboratory tests, median (IQR)			
Platelet counts (10^9/L)	75.00 (62.25)	74.00 (63.00)	79.00 (61.00)
AST (U/L)	35.00 (25.50)	36.00 (38.00)	33.00 (29.70)
ALT (U/L)	25.00 (23.00)	25.00 (22.00)	27.00 (22.95)
Hemoglobin (g/L)	76.00 (30.00)	75.00 (30.00)	77.75 (30.30)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; IQR, interquartile range; SBP, systolic blood pressure.

of the 2 groups (Supplemental Table S1, http://links.lww.com/HC9/A275).

Univariate and multivariate analyses for cumulative probability of 5-day treatment failure

Univariate analyses of all patients before PSM demonstrated that Child-Pugh class (HR, 1.506; 95% CI: 1.145–1.981), alanine aminotransferase (HR, 1.000; 95% CI: 1.000–1.000), and aspartate aminotransferase (HR, 1.001; 95% CI: 1.000–1.001) were independently related to cumulative probability of 5-day treatment failure. On multivariable analysis, Child-Pugh class (HR, 1.468; 95% CI: 1.115–1.932) was the independent risk factor of cumulative probability of 5-day treatment failure (Supplemental Table S3, http://links.lww.com/HC9/A275). After PSM, univariate analyses in all patients demonstrated that the Child-Pugh class (HR, 1.610; 95% CI: 1.094–2.372) was the independent risk factor related to 5-day treatment failure (Table 2).

Five-day treatment failure

Before PSM, the incidence of 5-day treatment failure was 3.7% in the urgent endoscopy group and 2.9% in the early group ($p = 0.24$) (Supplemental TableS4, Supplemental Figure S2, http://links.lww.com/HC9/A275). After PSM, the incidence of 5-day treatment failure was 3.0% in the urgent endoscopy group and 2.9% in the early group ($p = 0.90$) (Table 3, Figure 1)

In the subgroup analysis, among patients with Child-Pugh class *B*, the 5-day treatment failure rate was 3.9% in the urgent endoscopy group and 1.7% in the early endoscopy group before PSM ($p = 0.02$) (Supplemental Figure S3, http://links.lww.com/HC9/A275), whereas 4.0% in the urgent endoscopy group and 1.7% in the early endoscopy group after PSM ($p = 0.03$) (Figure 2). Among the patients with Child-Pugh *A*, the 5-day treatment failure rate was 2.6% in the urgent endoscopy group and 2.8% in the early endoscopy group before PSM ($p = 0.63$) (Supplemental Figure S3, http://links.lww.com/HC9/A275), whereas 3.7% in the urgent endoscopy group and 2.8% in the early endoscopy group after PSM ($p = 0.82$) (Figure 2). Among the patients with Child-Pugh *C*, the 5-day treatment failure rate was 12.2% in the urgent endoscopy group and 9.8% in the early endoscopy group before PSM ($p = 0.20$) (Supplemental Figure S3, http://links.lww.com/HC9/A275), whereas 11.3% in the urgent endoscopy group and 9.8% in the early endoscopy group after PSM ($p = 0.30$) (Figure 2).

Among the patients with a first episode of bleeding, the 5-day treatment failure rate was 5.3% in the urgent endoscopy group and 3.4% in the early endoscopy group before PSM ($p = 0.68$) (Supplemental Figure S4, http://links.lww.com/HC9/A275), whereas 5.0% in the urgent endoscopy group and 3.4% in the early endoscopy group after PSM ($p = 0.83$) (Figure 3). Among the patients with a previous episode of bleeding, the 5-day treatment failure rate was 6.5% in the urgent endoscopy group and 3.4% in the early endoscopy group before PSM ($p = 0.31$) (Supplemental Figure S4, http://links.lww.com/HC9/A275), whereas 6.3% in the urgent endoscopy group and 3.4% in the early endoscopy group after PSM ($p = 0.15$) (Figure 3)

TABLE 2 Univariate analysis of 5-day treatment failure after PSM analysis

	Univariate analysis	
	HR (95% CI)	*p*
Age	1.007 (0.984–1.031)	0.556
Sex (M)	0.986 (0.551–1.764)	0.962
SBP	0.996 (0.981–1.011)	0.615
Heart rate	1.012 (0.998–1.027)	0.102
With a bleeding history	1.146 (0.673–1.953)	0.616
Child-Pugh class	1.610 (1.094–2.372)	0.016
Platelet counts	0.999 (0.996–1.003)	0.779
AST	1.000 (0.999–1.000)	0.986
ALT	1.001 (1.000–1.003)	0.172
Hemoglobin	1.000 (0.988–1.011)	0.934

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; PSM, propensity score matching; SBP, systolic blood pressure.

In-hospital mortality

The in-hospital mortality was 2.8% in the urgent endoscopy group and 1.2% in the early endoscopy group ($p < 0.05$) (Supplemental Table S4, http://links.lww.com/HC9/A275). After PSM, the in-hospital mortality was 1.9% in the urgent endoscopy group and 1.2% in the early endoscopy group ($p = 0.26$) (Table 3).

In subgroup analysis, among the patients with bleeding history, the in-hospital mortality was 3.0% in the urgent endoscopy group and 1.0% in the early endoscopy group ($p < 0.05$). After PSM, the in-hospital mortality was 1.6% in the urgent endoscopy group and 1.0% in the early endoscopy group ($p = 0.58$). Among the patients with Child-Pugh class *A* (before PSM, $p = 0.45$; after PSM, $p = 1.00$), Child-Pugh class *B* (before PSM, $p = 0.66$; after PSM, $p = 0.05$), Child-Pugh class *C* (before PSM, $p = 0.12$; after PSM, $p = 0.44$), or a first bleeding episode (before

TABLE 3 Outcome in patients receiving urgent (< 6 h) versus early (6–24 h) endoscopy after PSM

Outcome	Urgent endoscopy group (n = 935); n (%)	Early endoscopy group (n = 935); n (%)	*p*
Primary outcome			
Treatment failure	28 (2.99)	27 (2.89)	0.901
Secondary outcome			
Death	18 (1.93)	11 (1.18)	0.260
Need for ICU	170 (18.20)	200 (21.39)	0.107
Length of hospital stay, mean (SD)	17.86 (11.22)	12.90 (9.68)	< 0.001

Abbreviations: ICU, intensive care unit; PSM, propensity score matching.

PSM, $p = 0.13$; after PSM, $p = 1.00$), the in-hospital mortality was similar between the urgent endoscopy group and the early endoscopy group.

Need for intensive care unit and the length of hospital stay

The incidence of need for ICU was 22.3% in the urgent endoscopy group and 21.5% in the early endoscopy group ($p = 0.56$) (Supplemental Table S4, http://links.lww.com/HC9/A275). The mean length of hospital stay was 16.3 days in the urgent endoscopy group and 12.9 days in the early endoscopy group ($p < 0.05$) (Supplemental Table S4, http://links.lww.com/HC9/A275). After PSM, the incidence of need for ICU was 18.2% in the urgent endoscopy group and 21.4% in the early endoscopy group ($p = 0.11$) (Table 3). The mean length of hospital stay was 17.9 days in the urgent endoscopy group and 12.9 days in the early endoscopy group ($p < 0.05$) (Table 3).

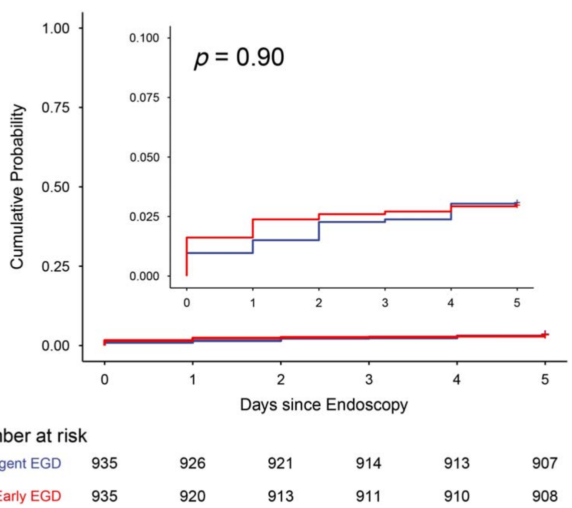

FIGURE 1 Cumulative probability of 5-day treatment failure in all patients with cirrhosis after PSM analysis. Abbreviations: EGD, esophagogastroduodenoscopy; PSM, propensity score matching.

The 5-day treatment failure incidence and the in-hospital mortality in patients with endoscopy performed <2 hours and 12–24 hours

There were 2678 patients with endoscopies performed <12 hours and 641 patients with endoscopies performed from 12 to 24 hours. The baseline characteristics of the patients are shown in Supplemental Table S2 (http://links.lww.com/HC9/A275). SBP, platelet count, and alanine aminotransferase showed no difference between the 2 groups. Age, male sex, heart rate, bleeding history, Child-Pugh class, aspartate aminotransferase, and hemoglobin were significantly different between the 2 groups. After PSM, 641 patients were analyzed in each of the 2 groups.

Before PSM, the incidence of 5-day treatment failure was 4.0% in the <12-hour group and 2.2% in the 12–24 hours group ($p = 0.04$). After PSM, the incidence of 5-day treatment failure in the <12-hour group was 2.3% and 2.2% in the 12–24 hours group ($p = 0.85$).

Before PSM, the in-hospital mortality was 5.8% in the <12-hour group and 0.5% in the 12–24 hours group ($p < 0.05$). After PSM, the in-hospital mortality was 2.2% in the <12-hour group and 0.5% in the 12–24 hours group ($p < 0.05$).

DISCUSSION

The present study, to our best knowledge, is the largest cohort of patients undergoing emergency endoscopy for AVB and is the first to report on the appropriate timing of endoscopy intervention for AVB defined by the incidence of treatment failure within 5 days and in-hospital mortality. After PSM analysis, the overall results indicated that the timing of endoscopy (< 6 h or 6–24 h) made no difference in either the incidence of treatment failure within 5 days or the in-hospital mortality among patients with cirrhosis with AVB. In addition, we performed an additional analysis, in which we compared the 5-day treatment failure incidence and the in-hospital mortality among patients with endoscopy performed <12 hours and 12–24 hours. The results

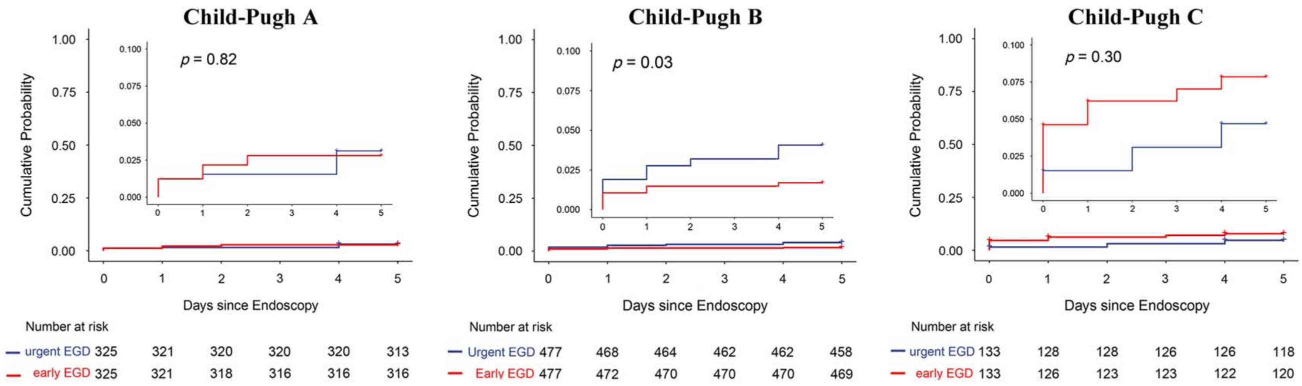

FIGURE 2 Cumulative probability of 5-day treatment failure in patients with cirrhosis with Child-Pugh *A*, *B*, or *C* after PSM analysis. Abbreviations: EGD, esophagogastroduodenoscopy; PSM, propensity score matching.

demonstrated that the timing of endoscopy (< 12 h or 12–24 h) made no difference in the incidence of treatment failure within 5 days, and the in-hospital mortality was higher in the <12-hour group than that in the 12–24 hours group of patients with cirrhosis with AVB.

Although experts suggest performing endoscopy as soon as possible for AVB, the optimal timing of endoscopic therapy for AVB remains controversial. Some prior studies suggest a benefit of early endoscopy (variably defined) on mortality, whereas others do not[10]. In addition, present expert consensus and guidelines recommended endoscopy within 12 hours for all patients suspected of having AVB[18,19]. However, a limitation of previous studies was that they presented unadjusted comparisons and our study in a large nationwide cohort did propensity matching and adjustment with multivariable analysis to show that the difference in the incidence of 5-day treatment failure between urgent endoscopy group (timing of endoscopy <6 h after admission) and the early endoscopy group (timing of endoscopy 6–24 h after admission) was not statistically significantly different ($p = 0.24$), and the results remained unchanged after PSM analysis ($p = 0.90$). In addition, treatment failure tended to be higher with endoscopy <12 hours versus 12–24 hours (2.3% vs 2.2%), suggesting endoscopy within 12 hours is unlikely to improve this outcome.

Various risk factors for rebleeding and in-hospital mortality have been reported. For example, the presence of hematemesis, delayed endoscopy for more than 15 hours, high Model for end stage liver disease (MELD) score, and failure of the first endoscopy to achieve hemostasis are independent risk factors for in-hospital mortality in patients with cirrhosis with AVB[10]. Moreover, the results of another study suggest that low-risk patients (MELD core <17) may not benefit from urgent endoscopy in terms of 6-week rebleeding and mortality[11]. The severity of the underlying liver disease seems to be more predictive of prognosis and could, therefore, help to classify patients into different risk strata, opening the possibility of individualizing treatment strategies for patients with AVB[20–22]. In addition, the platelet-albumin-bilirubin score on admission was a

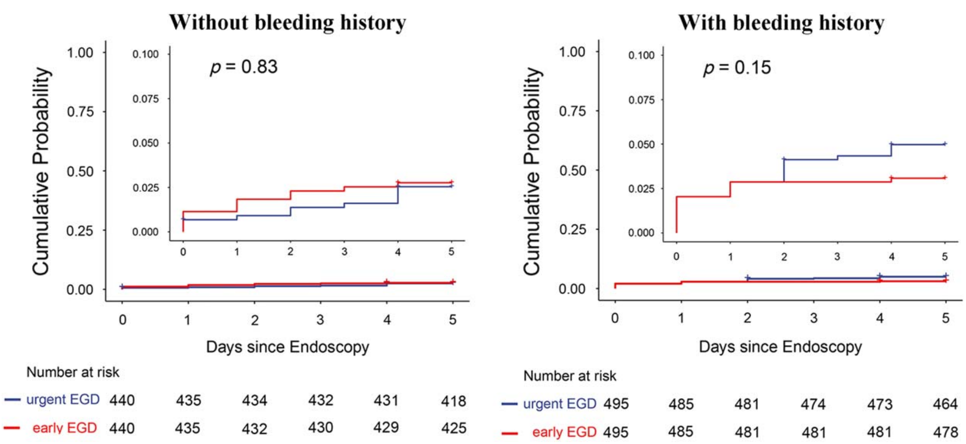

FIGURE 3 Cumulative probability of 5-day treatment failure in patients with cirrhosis without or with bleeding history after PSM analysis. Abbreviations: EGD, esophagogastroduodenoscopy; PSM, propensity score matching.

good prognostic indicator for patients with AVB and predicted early mortality and rebleeding[23–26].

Our study, in addition, revealed in subgroup analysis that among patients with Child-Pugh class *B*, urgent endoscopy within 6 hours seemed to be associated with an increased rate of treatment failure (before PSM, $p = 0.007$; after PSM, $p = 0.016$). Although caution should be exercised when interpreting the result, these data raise the possibility that the current recommendation of performing endoscopy as soon as possible may not be optimal for all patients with AVB, especially patients with Child-Pugh *B*. Possible explanations for this result include the following: first, urgent endoscopy may be associated with suboptimal resuscitation; sufficient time for pre-endoscopic optimization of the patient's clinical state may be more important than very early endoscopy. Second, the quality of the endoscopic examination and therapy may be suboptimal in the setting of urgent endoscopy due to the remaining food and blood in the stomach. It is also notable that in patients with Child-Pugh *C*, although patients having urgent endoscopy also had a higher 5-day treatment failure incidence, the difference in treatment failure was statistically insignificantly different after PSM, perhaps owing to the small sample size (135/935, 14.4%). Further study on this topic is warranted, particularly in patients with more advanced liver diseases.

Several limitations of the study are notable. First, data from this nationwide cohort were acquired retrospectively and, therefore, could lead to selection bias and lack of management details. Although this weakness is likely offset by the implementation of rigorous methodology to identify patients with AVB and define bleeding, and by the inclusion of a very large sample size, prospective studies should be conducted to further evaluate the impact of urgent endoscopy on patients with AVB. Second, most of our patients had a background of hepatitis *B* virus-related cirrhosis, which reflects the current real-world situation in many parts of Asia-Pacific regions. Whether the results obtained in this study can be extrapolated to hepatitis *C* virus, alcohol, or non–alcohol-associated steatohepatitis-related cirrhosis is not certain. Lastly, given the design of the study, we could only define the incidence of treatment failure within 5 days and in-hospital mortality as outcomes. Long-term follow-up and overall survival should be explored further.

In conclusion, the data suggest that the performance of endoscopy within 6–12 or within 24 hours of presentation among patients with cirrhosis with AVB led to similar treatment failure outcomes.

AUTHOR CONTRIBUTIONS

Xiaolong Qi: study concept and design. Wenhui Zhang, Huiling Xiang, LiYao Zhang, Chuan Liu, Lili Yuan, Lijun Peng, Min Gao, Chuanzhu Lv, Dongli Xia, Xing Wang, Jia Li, Ying Song, Xiqiao Zhou, Xingsi Qi, Jing Zeng, Xiaoyan Tan, Mingming Deng, Haiming Fang, Shenglin Qi, Song He, Yongfeng He, Bin Ye, Wei Wu, Tong Dang, Jiangbo Shao, Wei Wei, Jianping Hu, Xin Yong, Chaohui He, Jinlun Bao, Yuening Zhang, Guo Zhang, Rui Ji, Yang Bo, Shengjuan Hu, Wei Yan, Hongjiang L, Yong Wang, Yanling Wang, Mengmeng Li, Jia Lian, Chang'en Liu, Yunhai Wu, Ye Gu, Yan Wang, Ping Cao, Shuni Tian, Lin Lu, Yanfei Fang, Pan Jiang, Zhenbei Liu, Aimin Liu, Bin Wu, Lili Zhao, Shuang Li, Jinggui Qiao, Lihui Sun, Mengyu Li, Chengwen, Fang, Hao Chen, Zibin Tian, Gaoyang Lin, Xuanhui Huang, Jitao Chen, Ying Deng, Muhan Lv, Jingyuan Liao, Lijiu Zhang, Junyu Lu, Suhua Wu, Xiaocui Yang, Wenwei Guo, Jianbo Wang, Chao Chen, Erjiong Huang, Limei Ren, Hongduo Pan, Yuehua Yu, Ming Yang, Shuangping Cheng, Yangyang, Xiaoli Wu, Limaocai Rang, Yunxiao Liang, Ping Han, Yanmin Zhang, and Fengmei Wang: acquisition of data and technique support. Yifei Huang and Chuan Liu: analysis and interpretation of data. Xiaolong Qi, Yifei Huang, and Xiuping Zhang: drafting of the manuscript. Xiaolong Qi, Mark Edward McAlindon, Wai-Kay Seto, and Don C. Rockey: critical revision of the manuscript. All authors have read and approved the final manuscript.

CONFLICTS OF INTEREST

The authors have no conflicts to report.

DATA AVAILABILITY

Deidentified individual participant data will not be shared. The study protocol is included as a data supplement, http://links.lww.com/HC9/A275 available with the online version of this article.

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