Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Delayed endoscopy increases re-bleeding and mortality in patients with hematemesis and active esophageal variceal bleeding: A cohort study

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Background & Aims: Active bleeding is a poor prognostic indicator in patients with acute esophageal variceal bleeding. This study aimed at determining indicators of 6-week re-bleeding and mortality in patients with "active" esophageal variceal bleeding, particularly emphasizing the presenting symptoms and timing of endoscopy to define the treatment strategy.

Methods: From July 2005 to December 2009, cirrhotic patients with endoscopy-proven active esophageal variceal bleeding were evaluated. Cox proportional hazards regression analysis was used to determine the indicators of 6-week re-bleeding and mortality. Outcome comparisons were performed by Kaplan–Meier method and log rank test.

Results: In 101 patients, the overall 6-week and 3-month re-bleeding rates were 25.7% (n = 26) and 29.7% (n = 30), respectively. The overall 6-week and 3-month mortality was 31.7% (n = 32) and 38.6% (n = 39), respectively. Door-to-endoscopy time (hr), MELD score, and portal vein thrombosis were indicators of 6-week re-bleeding, while hematemesis upon arrival, MELD score, and hepatocellular carcinoma were indicators of 6-week mortality. Overall mortality was poorer in hematemesis than in non-hematemesis patients (39.7% *vs.* 10.7%, $p = 0.007$). In hematemesis patients, 6-week re-bleeding rate (18.9% *vs.* 38.9%, $p = 0.028$) and mortality (27% *vs.* 52.8%, $p = 0.031$) were lower in those with early ($\leqslant$12 h) than delayed (>12 h) endoscopy. In non-hematemesis patients, early and delayed endoscopy had no difference on 6-week re-bleeding rate (17.6% *vs.* 18.2%, $p = 0.944$) and mortality (11.8% *vs.* 9.1%, $p = 0.861$).

Conclusions: It is likely that early endoscopy ($\leqslant$12 h) is associated with a better outcome in hematemesis patients, but a randomized trial with larger case numbers is required before making a firm conclusion.

Keywords: Cirrhosis; Portal hypertension; Variceal bleeding; Prognosis; Predictor; Ligation.

Received 21 May 2012; received in revised form 11 July 2012; accepted 18 July 2012; available online 8 August 2012

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Introduction

Esophageal variceal bleeding (EVB) is one of the most life-threatening complications of liver cirrhosis [1,2]. Despite advances in management and therapy, mortality with each episode of EVB is still about 20–25% [3,4]. Several prognostic indicators, including the Child-Turcotte-Pugh (CTP) score, the model for end-stage liver disease (MELD) score, active bleeding at endoscopy, hypovolemic shock, hepatic venous pressure gradient, hepatocellular carcinoma (HCC), portal vein thrombosis, serum bilirubin, and creatinine and albumin levels, have been identified to predict mortality after EVB [5–8]. However, most risk factors are derived from studies without fulfilling the recent standard therapeutic protocol of prophylactic antibiotics and combination vasoactive agents, endoscopic ligation and subsequent non-selective beta-blocker for secondary prevention.

Active bleeding, either spurting or oozing from esophageal varices at endoscopy, occurs in 10–68% of EVB patients [9–13], and is persistently identified as an important predictor of failure to control bleeding, early re-bleeding, and mortality [4,5,14–16]. However, further assessment of the prognostic indicators in such high-risk patients is not determined.

The optimal timing of endoscopic treatment for EVB patients is empirical. Current guidelines of major professional societies recommend that endoscopy should be performed as soon as possible (within 12 h of admission) in cirrhotic patients with EVB, but the suggestion is based on expert opinion and requires corroborating evidence [2].

Table 1. Clinical characteristics of patients with active esophageal variceal bleeding.

Variables	Overall (n = 101)	Hematemesis (n = 73)	Non-hematemesis (n = 28)	*p* value
Gender (% male)	85 (84%)	62 (85%)	23 (82%)	0.765
Age (yr) (IQR)	57 (49-75)	57 (49-74.5)	60 (49-75)	0.946
Etiology of liver disease, n (%)				
Viral hepatitis (HBV, HCV)	74 (73%)	54 (74%)	20 (72%)	0.994
Alcohol	18 (18%)	12 (16%)	6 (21%)	0.570
Others	9 (9%)	7 (10%)	2 (7%)	1.000
CTP score (IQR)	9 (7.5-11)	9 (8-11)	8.5 (6-10.8)	0.323
MELD score (IQR)	13 (10-20)	13 (10-21.5)	12.5 (9.3-18)	0.477
Spurting/oozing	53/48 (53/47%)	38/35 (52/48%)	15/13 (54/46%)	1.000
Variceal size, ≤F2/F3, n (%)	56/45 (55/45%)	37/36 (51/49%)	19/9 (68/32%)	0.274
Gastric varices, n (%)	21 (20.8%)	17 (23%)	4 (14%)	0.469
SBP (mmHg) (IQR)	109 (93-135)	104 (90-124)	135 (105-144)	0.001
Heart rate (bpm) (IQR)	96 (85-108.5)	97 (85-109.5)	96 (82.8-107.8)	0.903
Shock, n (%)	21 (20.8%)	20 (27.4%)	1 (3.6%)	0.018
Ascites, n (%)	76 (75.2%)	56 (77%)	20 (71%)	0.769
Encephalopathy, n (%)	33 (32.7%)	26 (36%)	7 (25%)	0.435
Hct (%) (IQR)	27.9 (23.6-31.9)	27.5 (23.5-31.8)	28.4 (23.6-32.2)	0.823
Total bilirubin (mg/dl) (IQR)	1.9 (1.2-3.5)	1.9 (1.1-3.9)	2.0 (1.2-3.0)	0.844
AST (U/L) (IQR)	50.5 (34.5-94)	50 (32-128.5)	52 (39-78)	0.813
ALT (U/L) (IQR)	44.5 (28-80.8)	45 (26.5-91.5)	38.5 (28.3-64.8)	0.519
Creatinine (mg/dl) (IQR)	1.0 (0.8-1.6)	1.0 (0.8-1.7)	1.0 (0.9-1.4)	0.629
Albumin (g/dl) (IQR)	2.9 (2.4-3.3)	2.9 (2.4-3.3)	2.9 (2.4-3.2)	0.843
INR (IQR)	1.26 (1.12-1.45)	1.26 (1.14-1.46)	1.25 (1.09-1.45)	0.541
Platelet (10^3/mm^3) (IQR)	111 (67.5-160.5)	111 (66.5-165.5)	111 (90.8-150)	0.685
PRBCs (unit) (IQR)	3 (2-7)	5 (3-7.5)	2 (2-3)	0.001
Infection, n (%)	34 (33.7%)	24 (33%)	10 (36%)	0.972
HCC, n (%)	47 (46.5%)	35 (48%)	12 (43%)	0.813
Portal vein thrombosis, n (%)	25 (24.8%)	20 (27%)	5 (18%)	0.461

Values given are median values and inter-quartile range (IQR).
The *p* value was compared between hematemesis and non-hematemesis.
HBV, hepatitis B virus; HCV, hepatitis C virus; CTP, Child-Turcotte-Pugh; MELD, model for end-stage liver disease; SBP, systolic blood pressure; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PRBCs, packed red blood cells (250 ml per unit); HCC, hepatocellular carcinoma.

The aim of this study is to determine the prognostic indicators of 6-week re-bleeding and mortality in patients with "active" EVB on current standard treatment, with particular emphasis on presenting symptoms and timing of endoscopy.

Materials and methods

Patients

From July 2005 to December 2009, cirrhotic patients who presented at our hospital with suspected EVB were referred to the portal hypertension team of our hospital. If active EVB was proven by endoscopy, the patient was invited to enter the cohort. The exclusion criteria were (1) age <18 years; (2) terminal illness of a major organ (e.g., severe heart failure, chronic obstructive pulmonary disease, and malignancy except HCC); and (3) treatment of acute variceal bleeding (i.e., vasoactive agents or endoscopic treatment) in another hospital, (4) history of variceal bleeding and receiving ligation within three months. The diagnosis of liver cirrhosis was based on liver biopsy or the combination of clinical, biochemical, and imaging findings. The diagnosis of HCC was based on history or combined typical dynamic imaging appearance and elevated α-fetoprotein (AFP). Patients who did not receive regular esophageal variceal ligation (EVL) or were lost to follow-up, within three months following EVB, were also excluded. The hospital's Institutional Review Board approved the study.

Endoscopic treatment procedures

A vasoactive agent with somatostatin was administered for three days and a prophylactic antibiotic was given for five days upon the patient's arrival. Packed red blood cell (PRBC) was given to maintain hemoglobin of 8 g/dl. Endoscopy was performed as soon as possible and the timing depended on the patients' or family's will, informed consent, availability of endoscopist, and first aid for resuscitation if there was unstable hemodynamic status. The EVL was performed by two experienced endoscopists, using an Olympus XQ-260 video-endoscope (Olympus Optical Co., Tokyo, Japan) with endoscopic ligating devices (Bard International Products, Tewksbury, MA), and an overtube, or multiband ligators (Wilson-Cook Medical, Winston-Salem, NC). No more than 10 rubber bands were used in each session.

Clinical assessment and follow-up

Information regarding presentation of EVB was carefully gathered from the patients and their families. A nasogastric tube was inserted for diagnosis before endoscopy in patients without hematemesis or coffee ground vomitus.