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ORIGINAL ARTICLE

The risk of variceal bleeding during endoscopic retrograde cholangiopancreatography

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Abstract

Background: Endoscopic retrograde cholangiopancreatography (ERCP) is a widely performed procedure. However, the risk of variceal bleeding during ERCP has rarely been assessed. This study aims to evaluate the risk of variceal bleeding in patients with esophageal varices (EV) undergoing ERCP.

Methods: From October 2010 to November 2017, the study retrospectively enrolled 75 cirrhotic patients who received elective ERCP. The patient's risk of gastrointestinal (GI) and variceal bleeding and other procedure-related adverse events within 30 days of ERCP were evaluated.

Results: Among the 75 patients, 45 patients (60.0%) had EV. Most of the patients were males (65.3%), and there were high rates of viral hepatitis B-related cirrhosis (36.0%), Child-Pugh B (49.3%), and an indication of choledocholithiasis (40.0%). Thirty-three of 45 (73.3%) patients had high-risk EV, and nine (20.0%) patients had concomitant gastric varices. There was no esophageal variceal bleeding; however, one patient had gastric variceal bleeding after ERCP. Nonvariceal significant GI bleeding occurred in three patients with EV and one without EV ($p = 0.529$). Post-ERCP pancreatitis occurred in three patients with EV and five without EV ($p = 0.169$). No perforation or procedure-associated mortality was noted.

Conclusion: The risk of esophageal variceal bleeding within 30 days of ERCP is neglectable, except for a patient who suffered from gastric variceal bleeding. Other complications, such as nonvariceal bleeding and pancreatitis, are also no higher in patients with EV. Therefore, ERCP is generally a safe procedure for a patient with high-risk esophageal varices.

Keywords: Endoscopic retrograde cholangiopancreatography; Esophageal varices; Gastric varices; Variceal bleeding

1. INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) has been a reliable and widely accepted procedure for pancreaticobiliary disease since it was first reported in 1968.[1] However, ERCP continues to be associated with several adverse events, which are attributed to the procedural invasiveness.[2,3] Due to the blind insertion of duodenoscope and coagulation abnormality as well as thrombocytopenia in patients with liver cirrhosis, variceal bleeding precipitated by ERCP is a major concern, but there is no robust evidence to highlight the risk.

Esophageal variceal bleeding was one of the major complications of liver cirrhosis and had a 6-week mortality rate between 15% and 25% despite the advancement of treatment.[4–7] A previous study showed no event of esophageal variceal bleeding in 23 cirrhotic patients undergoing ERCP. The overall procedure-associated bleeding risk was 13.5% in cirrhotic patients, regardless of the existence of esophageal varices (EV).[8] The other four studies enrolled cirrhotic patients who received ERCP and reported rates of procedure-associated bleeding of 1.1%, 2.3%, 2.5%, and 5.7%, respectively.[9–12] However, these studies were focused on the overall adverse events in cirrhotic patients without special emphasis on the etiology of bleeding, especially variceal bleeding, or making comparisons to patients without varices. Therefore, clarifying the risk of variceal bleeding precipitated by ERCP is important.

Here, we compare the risk of post-ERCP variceal bleeding as well as other adverse events between cirrhotic patients with and without EV.

2. METHODS

2.1. Patients

This study is a retrospective study. A total of 4445 cases who received ERCP were screened from October 2010 to November 2017, and 75 adult patients with liver cirrhosis were enrolled in a single tertiary medical center. Data were collected within 30 days of the procedure.[13] The diagnosis of liver cirrhosis was based on liver biopsy or clinical, biochemical, and radiological findings. The decompensation of liver cirrhosis was defined by

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the presence of ascites, variceal bleeding, encephalopathy, and/or jaundice.[14] The study was performed in accordance with the Declaration of Helsinki and current ethical guidelines. It was also approved by the Institutional Review Board (2021-06-005AC).

2.2. Endoscopic evaluation

The size of EV was recorded following the criteria proposed by Beppu et al[15] small and straight varices were recorded as F_1, moderately sized and tortuous varices were recorded as F_2, and large and tumorous varices were recorded as F_3. The EV size of F_2, F_3, and F_1 with red-color signs or Child-Turcotte-Pugh C hepatic reserve were defined as high-risk EV.[5,16]

2.3. Standard of medical care and procedure

The indications for ERCP, liver function tests, and image studies, including abdominal sonography, computer tomography, or magnetic resonance imaging of all the patients before the procedure, were evaluated by experienced endoscopists, gastroenterologists, and radiologists. Premedication with local pharyngeal 10% lidocaine spray and intravenous injection of midazolam and hyoscine-N-butylbromide were routinely prescribed if there was no contraindication. Antibiotic prophylaxis was not given. Therapeutic interventions were performed when indicated, such as endoscopic sphincterotomy, endoscopic papillary balloon dilation, endoscopic retrograde biliary drainage, and nasobiliary drainage. All patients under antiplatelet therapy stopped 7 days before the procedure. The patient under warfarin therapy was discontinued 5 days before the procedure with low-molecular-weight heparin bridging therapy and gave the last dose 24 hours before the procedure.

2.4. Definition of bleeding

Overall gastrointestinal (GI) bleeding is defined as any signs of bleeding from the GI tract, including endoscopic and clinical findings. Clinically significant GI bleeding was defined as clinical evidence of melena or hematemesis, with hemoglobin level dropping by more than 2 g/dL or the need for blood transfusion.[13,17] The definition of variceal bleeding was patients with clinical manifestations of GI bleeding, such as hematemesis, coffee-ground vomitus, hematochezia, or melena with endoscopic evidence of active bleeding, including adherent blood clots or erosions on varices and/or large varices with a red-color sign in the absence of other sources of bleeding.

2.5. Statistical analysis

The baseline characteristics to be evaluated with outcomes were selected and expressed as mean ± standard deviation for parametric variables or median ± interquartile range for nonparametric variables. The Mann-Whitney *U* test and independent *t* test were used for nonparametric variables and parametric variables, respectively. Pearson's chi-square analysis or Fisher's exact test were used to compare categorical variables, as appropriate. Multivariate analysis was done with those variables returning a $p < 0.1$ in the univariate analyses. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA).

3. RESULTS

3.1. Baseline clinical characteristics

Among the 75 patients study population, 60.0% patients (n = 45) had EV and 40.0% patients (n = 30) had no EV. The demographic characteristics of the study population are shown in Table 1.

Table 1

Baseline characteristics of patients

	Total	EV	No EV	
Baseline characteristics	n = 75	n = 45	n = 30	*p*
Age, median (range), y	62.1 ± 1.3	60.3 ± 1.7	64.8 ± 2.0	0.101
Sex (male), n (%)	49 (65.3)	29 (64.4)	20 (66.7)	0.843
Etiology, n (%)				
HBV	27 (36.0)	15 (33.3)	12 (40.0)	0.556
HCV	17 (22.7)	12 (26.7)	5 (16.7)	0.311
Alcohol	8 (10.7)	5 (11.1)	3 (10.0)	0.879
Others[a]	23 (30.7)	13 (28.9)	10 (33.3)	0.683
Child-Turcotte-Pugh classification, n (%)				
A	24 (32.0)	12 (26.7)	12 (40.0)	0.225
B	37 (49.3)	22 (48.9)	15 (50.0)	0.925
C	14 (18.7)	11 (24.4)	3 (10.0)	0.116
MELD score	15 (11–19)	15 (12–19)	15 (10–16)	0.219
HCC, n (%)	27 (36.0)	17 (37.8)	10 (33.3)	0.694
Other malignancy, n (%)	7 (9.3)	5 (11.1)	2 (6.67)	0.517
Chronic kidney disease, n (%)	7 (9.3)	3 (6.7)	4 (13.3)	0.331
End-stage renal disease, n	0	0	0	n/a
Using of antithrombotic agent, n (%)[b]	8 (10.7)	4 (8.9)	4 (13.3)	0.541
Serum lab data				
Prothrombin time, INR	1.21 (1.06–1.29)	1.22 (1.17–1.28)	1.20 (1.05–1.21)	0.075
Platelet count, K/cumm	89 (70–153)	83 (69–127)	120 (78–165)	0.055
Creatinine, mg/dL	0.90 (0.76–1.20)	0.85 (0.73–1.13)	0.99 (0.76–1.26)	0.747
ALT, U/L	49 (30–145)	51 (29–143)	47 (30–165)	0.893
AST, U/L	70 (42–128)	71 (43–131)	65 (39–116)	0.395
Albumin, g/dL	3.4 (2.8–3.7)	3.3 (2.9–3.7)	3.4 (2.8–3.7)	0.894
Total bilirubin, mg/dL	2.8 (1.4–7.7)	3.4 (1.5–11.0)	2.2 (1.2–5.0)	0.057

ALT = alanine transaminase; AST = aspartate transaminase; EV = esophageal varices; HBV = hepatitis B virus; HCV = hepatitis C virus; HCC = hepatocellular carcinoma; MELD = model for end-stage liver disease.
[a]Others etiology including three patients had autoimmune hepatitis, three patients had concomitant HBV infection and alcoholism, two patients had concomitant HBV and HCV infection, three patients had nonalcoholic steatosis hepatitis, three patients had primary biliary cholangitis, nine patients had cryptogenic cirrhosis.
[b]Seven patients using antiplatelet (four clopidogrel and three aspirin) and one patient using anticoagulant of warfarin.

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Table 2

Characteristic and prophylaxis of varices

	n = 45
EV size, n (%)[a]	
Trace	3 (6.7)
F1	17 (37.8)
F2	17 (37.8)
F3	8 (17.8)
Red-color signs, n (%)	18 (40.0)
High-risk EV, n (%)	33 (73.3)
Concomitant GV, n (%)	9 (20.0)
Primary prevention, n (%)	
EVL	16 (35.6)
NSBB	2 (4.4)
Secondary prevention, n (%)	
EVL + NSBB	9 (20.0)
EVL alone	3 (6.7)

EV = esophageal varices; EVL = endoscopic variceal ligation; GV = gastric varices; NSBB = nonselective beta-blocker.

[a]EV size defined as largest size of EV.

There is no difference in age, sex, etiology, model for end-stage liver disease (MELD) score, Child-Turcotte-Pugh, and serum biochemistry between patients with EV (EV group) and those without EV (non-EV group). Thirty-three of 45 (73.3%) patients had high-risk EV, and nine patients had concomitant gastric varices (GV). The characteristics of varices are shown in Table 2.

3.2. Indications and findings during the procedure

Indications of ERCP were choledocholithiasis (30/75, 40.0%), benign bile duct stricture (17/75, 22.7%), malignant tumor compression (9/75, 12.0%), cholecystitis (7/75, 9.3%), pancreatitis (6/75, 8.0%), and undetermined reasons (6/75, 8.0%). Successful cannulation was achieved in 72 (96.0%) patients, including 43 patients with EV and 29 patients without EV. Dilated common bile duct (CBD) was found in 17 patients (37.8%) with EV and 11 patients (36.7%) without EV. A negative ERCP result was detected in two patients (4.4%) with EV and one patient (3.3%) without EV. The number of patients undergoing therapeutic ERCP was also no different. About half of the patients received endoscopic balloon dilatation or endoscopic sphincterotomy. The details of therapeutic ERCP are shown in Table 3.

Table 3

Therapeutic interventions during endoscopic retrograde cholangiopancreatography

	EV	No EV	
	n = 45	n = 30	*p*
Therapeutic interventions, n (%)[a]			
EST	7 (15.6)	8 (26.7)	0.239
EPBD	13 (28.9)	7 (23.3)	0.594
ERBD	11 (24.4)	8 (26.7)	0.828
Plastic stent	6 (13.3)	5 (16.7)	0.689
Metallic stent	5 (11.1)	3 (10.7)	0.879
NBD	4 (8.9)	0 (0)	0.093

EPBD = endoscopic papillary balloon dilation; ERBD = endoscopic retrograde biliary drainage; ERCP = endoscopic retrograde cholangiopancreatography; EST = endoscopic sphincterotomy; NBD = nasobiliary drainage.

[a]One patient received EPBD and ERBD with metallic stent placement at the same time.

3.3. Bleeding related to the procedure

The risk of overall GI bleeding (5/45, 11.1% vs 3/30, 10.0%, $p = 0.879$) and significant GI bleeding (3/45, 6.7% vs 1/30, 3.3%, $p = 0.529$) was not different between patients with and without EV. However, a patient with EV experienced melena 2 days after endoscopic sphincterotomy and partial cover metallic stenting for distal CBD stricture (Fig. 1). Endoscopy disclosed gastric variceal bleeding at the posterior wall of the high body near the cardia (Fig. 2). He underwent endoscopic cyanoacrylate injection with N-butyl-2-cyanoacrylate for acute gastric variceal bleeding and endoscopic variceal ligation for EV. The patient was discharged 5 days later without further bleeding. Another patient experienced significant duodenal ulcer bleeding 7 days after ERCP. Endoscopic hemostasis was performed, which revealed a 0.8-cm Forrest class Ib ulcer located at the second portion of the duodenum and hemostasis was successfully achieved using epinephrine injection plus thermal therapy. The duodenal ulcer was not seen in the previous ERCP examination, and the patient did not use prophylaxis NSAID before and after ERCP. The details of the bleeding are shown in Table 4.

3.4. Other adverse events related to the procedure

Adverse events of ERCP were comparable between patients with EV and those without EV, regardless of counting by events (14 vs 11, $p = 0.659$) or patients (26.7% vs 36.7%, $p = 0.358$). The details of adverse events are shown in Table 5.

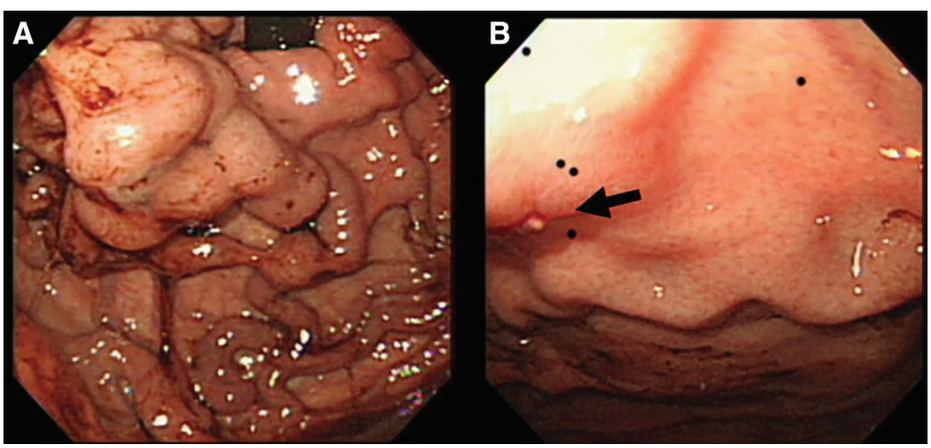

Fig. 1 Esophagogastroduodenoscopy findings. A, Tumor-like gastric varices at fundus and posterior wall of high body. B, A suspicious active oozing site at gastric varices (black arrow).

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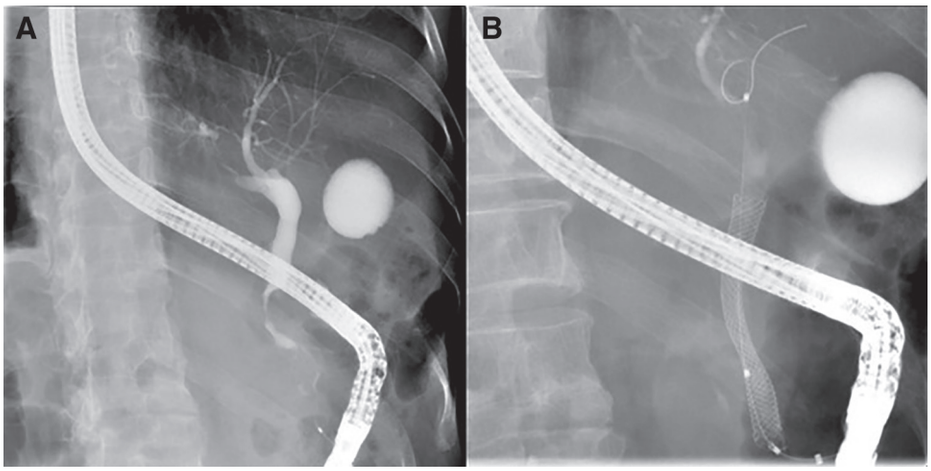

Fig. 2 Endoscopic retrograde cholangiopancreatography findings. A, A 4-cm narrowing at distal common bile duct in endoscopic retrograde cholangiography (ERC). B, A 6-cm partially covered metallic stent was deployed in ERC.

There was no procedure-related perforation or mortality during the study period.

3.5. Predictors of complications

On univariate and multivariate analyses, no indicator (including cirrhosis status, MELD score, age, sex, and hepatocellular carcinoma) could be identified to determine the adverse events (Supplementary Table 1, http://links.lww.com/JCMA/A158).

4. DISCUSSION

With regard to thrombocytopenia, coagulopathy, and potential comorbidity in patients with cirrhosis, these are major concerns for the occurrence of complications in the patients undergoing invasive procedures, particularly when ERCP is performed for patients with EV. In the literature, there are limited data regarding the adverse events in patients with concomitant cirrhosis and EV undergoing ERCP. Two previous retrospective cohort studies without special emphasis on EV demonstrated similar overall adverse events between cirrhotic and noncirrhotic patients.[8,9] Subgroup analysis showed an increased risk of adverse events only in patients with decompensated cirrhosis.[8,9] Nevertheless, another two studies showed increased overall adverse events in cirrhotic patients compared with noncirrhotic patients.[10,12] Therefore, the risk of an adverse event in patients with cirrhosis is controversial. Moreover, no study has focused on the influence of the existence of EVs. The serious concern of bleeding risk in patients with EV has never been well analyzed.

The lack of consistency in the definition of post-ERCP bleeding in cirrhotic patients might explain the wide range of bleeding rates in previous studies: from 1.1% to 13.5%.[8–12] In this study, the overall bleeding risk was 10.7% in the whole population, and the clinically significant GI bleeding risk was 5.3%, comparable with the previous study.[12] Again, details of EV, including the case number of patients with EV and high-risk EV, were not revealed in previous studies.[8–12] We found no esophageal variceal bleeding during and after diagnostic or therapeutic ERCP, even in those with high-risk EV. Interestingly, one patient with concomitant gastro-EV experienced gastric variceal bleeding 2 days after the procedure. It is possible that the side-view duodenoscope caused the unintended traumatic injury of gastric varix. Luckily, current treatment standards successfully controlled the acute bleeding, including antibiotic, vasoactive agent, and endoscopic cyanoacrylate injection with N-butyl-2-cyanoacrylate. Taken together, diagnostic or therapeutic ERCP is generally safe in patients with cirrhosis and EV.

According to five previous studies, the reported rates of post-ERCP pancreatitis in cirrhotic patients were from 4.4% to 8.3%. Only one previous study documented no prophylactic pharmacological therapy was used in that study.[12] Other prophylactic

Table 4

Characteristic of gastrointestinal bleeding

	EV	No EV	
	n = 45	n = 30	*p*
Overall GI bleeding	5 (11.1)	3 (10.0)	0.879
Variceal bleeding	1 (2.2)	0 (0)	0.411
Duodenal ulcer bleeding	1 (2.2)	0 (0)	0.411
Gastric Dieulafoy's lesion bleeding	1 (2.2)	0 (0)	0.411
Undetermined[a]	2 (4.4)	3 (10.0)	0.345
Clinically significant GI bleeding	3 (6.7)	1 (3.3)	0.529
Duodenal ulcer bleeding	1 (2.2)	0 (0)	0.411
Gastric Dieulafoy's lesion bleeding	1 (2.2)	0 (0)	0.411
Undetermined	1 (2.2)	1 (3.3)	0.770
Hb dropped, median (range), g/dL	1.8 (0.6–2.6)	2.3 (2.2–2.4)	0.836

GI bleeding = gastrointestinal bleeding; Hb = hemoglobin.

[a]One patient received upper and lower GI endoscopy and no bleeding source was noted in the EV group. Two patients in the no EV group and one patient in the EV group did not receive endoscopy for bleeding survey and improved after pharmacological therapy. Another patient in the no EV group did not perform endoscopy for bleeding survey and improved after blood transfusion and pharmacological therapy.

Table 5

Adverse events related to the procedure

	EV	No EV	
	n = 45	n = 30	*p*
Patients with adverse events, n (%)	12 (26.7)	11 (36.7)	0.358
Numbers of adverse events, total n	14	11	0.659
Characteristics of adverse events, n (%)			
Overall GI bleeding	5 (11.1)	3 (10.0)	0.879
Sepsis	6 (13.3)	5 (10.0)	0.689
Post-ERCP pancreatitis	3 (6.7)	3 (10.0)	0.602

ERCP = endoscopic retrograde cholangiopancreatography; EV = esophageal varices; GI bleeding = gastrointestinal bleeding.

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therapies, such as pancreatic duct stenting, were not well demonstrated in previous studies.[8–12] In this study, three patients received a prophylactic rectal nonsteroidal anti-inflammatory drug (two in the EV group and one in the no EV group), and one in the EV group received prophylactic pancreatic duct stenting for post-ERCP pancreatitis prophylaxis. Despite a small number of patients receiving prophylactic therapy for post-ERCP pancreatitis, the incidence rate of post-ERCP pancreatitis was 8.0% (6.7% in the EV group and 10.0% in the no EV group) in this study which is still comparable to previous studies.

No predictor of adverse events was consistently identified according to previous studies. Two studies reported decompensated cirrhosis as a risk factor,[9,10] but this was not confirmed in the third study.[12] In our study, decompensated cirrhosis was not a predictor of adverse events. This might be explained by the heterogenicity of populations, operator-dependable technique, and different definitions of adverse events.

This study has some limitations. First, selection bias cannot be prevented because of the study's retrospective nature. However, we believe the bleeding risk is very low, even if more than 70% of high-risk varices were included in this study. Second, the case number of this study is the largest among studies focused on varices. Nevertheless, this was not large enough to uncover the details of risk factors.

In conclusion, there was no difference in overall adverse events and GI bleeding between cirrhotic patients with and without EV receiving ERCP. Although ERCP is generally safe and esophageal variceal bleeding is rare even in patients with high-risk EV, particular attention should be paid to unintended injury of GV caused by side-view duodenoscope.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://links.lww.com/JCMA/A158.

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