

Useful Endoscopic Ultrasonography Parameters and a Predictive Model for the Recurrence of Esophageal Varices and Bleeding after Variceal Ligation

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Background/Aims: To identify the usefulness of endoscopic ultrasonography with a mini-probe (EUM) and to create a predictive model for esophageal variceal (EV) recurrence and bleeding following esophageal variceal ligation (EVL).

Methods: A total of 144 patients who received EUM prior to prophylactic EVL and met the inclusion criteria were enrolled. EUM findings, EV diameter, paraesophageal vein diameter, and the number of perforating veins were assessed.

Results: EV recurrence was observed in 42 patients (29.2%), 10 of whom experienced EV bleeding. Larger diameter of the paraesophageal vein (odds ratio [OR], 1.51; 95% confidence interval [CI], 1.17 to 1.96; $p=0.002$) and perforating vein (OR, 3.27; 95% CI, 1.11 to 9.65; $p=0.032$) were significant predictive factors for EV recurrence. However, the diameter of the paraesophageal vein was the only significant risk factor for EV bleeding (adjusted OR, 1.51; 95% CI, 1.06 to 2.16; $p=0.022$). The areas under the curves of the predictive model for EV recurrence and bleeding were 0.872 (95% CI, 0.811 to 0.934) and 0.811 (95% CI, 0.630 to 0.992), respectively.

Conclusions: The diameter of the paraesophageal vein was a significant predictive factor for EV recurrence and bleeding. The predictive model constructed based on the significant EUM findings exhibited good performance. (**Gut Liver 2017;11:843-851**)

Key Words: Esophageal and gastric varices; Recurrence; Hemorrhage; Endosonography

INTRODUCTION

Portal hypertension increases blood flow and engorgement of the collateral vessels surrounding the lower esophagus and proximal stomach, leading to a build-up of the gastroesophageal varices in approximately 50% of patients with cirrhosis.¹ Once varices have been diagnosed, variceal bleeding occurs at a yearly rate of 10% to 15%.² Esophageal variceal (EV) bleeding is associated with high morbidity and mortality in patients with cirrhosis. Treatment to prevent EV bleeding should be performed when large varices are present. Endoscopy should be considered for patients with compensated liver cirrhosis (LC) at every 2 to 3 years, and for patients with decompensated LC at every 1 to 2 years.³ Despite treatment improvements over the last decade, the overall mortality rate is 20% due to bleeding from EV.⁴ Either nonselective β -blocker or endoscopic band ligation is recommended for the prevention of the first variceal bleeding of medium or large varices. Also, combination of β -blockers and band ligation is the preferred therapy as it results in lower re-bleeding compared to either therapy alone.⁵ However, little is known about which patients are more prone to bleeding from EV or who need close management after EVL.

Endoscopic ultrasonography with a mini-probe (EUM) can be used to clearly visualize the vascular network around EV. The venous anatomy of the lower esophagus and upper stomach has been described in four layers, such as the intraepithelial channels, superficial venous plexus, deep venous plexus, and adventitial veins.^{6,7} The superficial venous plexus communicates with the deep venous plexus peri-esophageal collateral veins (peri-ECVs) and the para-esophageal collateral veins (para-ECVs)

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through the perforating veins. The peri-ECVs are located adjacent to the muscularis externa of the esophagus, and the para-ECVs are external to the esophageal wall, with no contact with the muscularis externa. EUM enables accurate measurements of para-ECV and EV sizes and the location of the perforating veins. The collateral deep veins seen on EUM are related to recurrence of EV.^{8,9} However, the role of EUM for predicting EV recurrence or bleeding after EVL have not yet been established. In this study, we aimed to identify significant EUM findings to construct a predictive model for EV recurrence and bleeding followed by prophylactic EVL.

MATERIALS AND METHODS

1. Study population

A total of 144 of 248 patients with EV who were consecutively examined by EUM at the Digestive Disease Center and Research Institute, Department of Internal Medicine, Soonchunhyang University School of Medicine, Bucheon, Korea from December 2008 to December 2014 and met the inclusion criteria were enrolled in this study (Fig. 1). The diagnosis of liver cirrhosis was based on histological or clinical factors. The inclusion criteria were EV grade \geq F2 as a prerequisite and a moderate to severe red color sign, according to the general rules for recording endoscopic findings of EV, proposed by the Japanese Society for Portal Hypertension;¹⁰ all EUM parameters could be evaluated, including diameter of EV, diameter of paraesophageal veins, and diameter of portal veins (PVs); and baseline laboratory data available. The exclusion criteria were: failure to eradicate EV or diagnosed or developed hepatocellular carcinoma; presence of peptic ulcer or inflammatory bowel

disease; concomitant main PV thrombosis; received balloon-occluded retrograde transvenous obliteration (BRTO) or transjugular intrahepatic portosystemic shunt (TIPS), EV bleeding history within 2 years prior to prophylactic EVL, death from other illness independent of liver disease, and lost to follow-up. Demographic data, including age, sex, etiology of cirrhosis, use of nonselective β -blocker, and previous episode of EV bleeding were collected. Platelet count, serum bilirubin and albumin, and prothrombin time were also examined. The severity of liver cirrhosis was graded by Child-Turcotte-Pugh (CTP) class and the Model for End-Stage Liver Disease score. Spleen size was examined by abdominal ultrasonography.

This study was approved by the Institutional Review Board (IRB) of Soonchunhyang University Bucheon Hospital (IRB number: 2015-07-022-001).

2. Measurement of endoscopic ultrasonographic parameters

All patients underwent EUM prior to EVL. The procedures were carried out by an endoscopist (S.G.K.) using a miniature ultrasonic probe (UM-2R, 12 MHz; Olympus, Tokyo, Japan). The endoscopy used for EUM was a GIF-2TQ 260M or a 2T240 (Olympus). The examinations were recorded on videotape so that an independent endoscopist (Y.S.K.) could review the EUM findings to avoid observer bias and discuss the images until they reached agreement. EV diameter, diameter of para-ECVs located external to the esophageal wall, diameter and number of perforating veins, and the presence of gastric varices were assessed as described previously.⁹ However, peri-ECVs were not evaluated entirely as many peri-ECVs occur in a single patient. The largest para-ECV that connected with EV through a perforating vein was selected as a valid parameter, but all visible

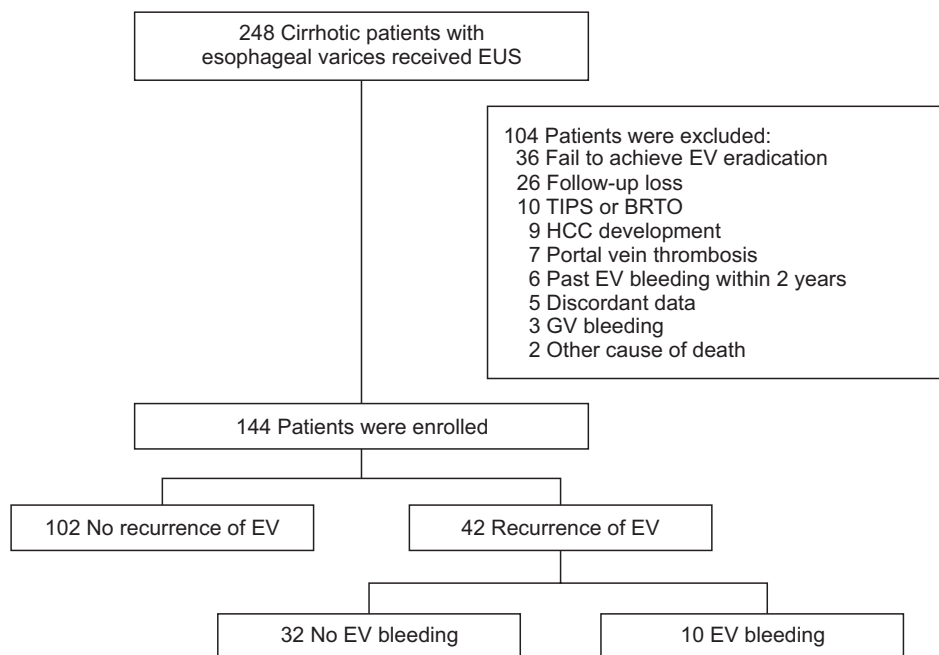


Fig. 1. Flow diagram for the study. EUS, endoscopic ultrasonography; EV, esophageal varices; TIPS, transjugular intrahepatic portosystemic shunt; BRTO, balloon-occluded retrograde transvenous obliteration; HCC, hepatocellular carcinoma; GV, gastric varices.

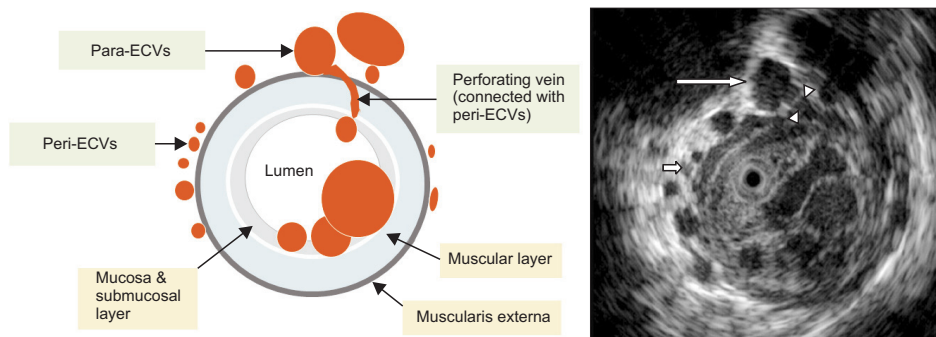


Fig. 2. A schematic diagram showing esophageal varices and vascular structures around the esophageal wall using endoscopic ultrasonography with a mini-probe. Long arrow, para-esophageal collateral veins (ECVs); short arrow, peri-ECVs; arrow head, perforating veins.

perforating veins were reported in terms of number and diameter. Esophageal varices and the vascular structures around the esophageal wall using EUM is shown as a schematic diagram in Fig. 2.

3. EVL procedure and follow-up

The EVL indication was based on the Baveno IV consensus.¹¹ The endoscope loaded with a multi-banding device (6-shooter; Wilson-Cook, Limerick, Ireland) was introduced into the esophagus, and each band was consecutively applied from the gastroesophageal junction to the oral side. All visible varices were ligated during each procedure. EVL was repeated at 2-month intervals until EV were eradicated completely. The obliteration of varices was defined as nonvisualization of varices on endoscopy. Prophylactic antibiotics and omeprazole were given to all patients, and a nonselective β -blocker was prescribed to patients with EV (\geq F2) who had not bled but had a high risk of hemorrhage (CTP class B/C or variceal red wale markings on endoscopy) to prevent the first variceal hemorrhage if they could tolerate a nonselective β -blocker. Follow-up endoscopy was performed at 6-month intervals for 1 year after obliteration of EV, and variceal bleeding, reappearance of EV (F1), or the presence of the red color sign was regarded as EV recurrence. Among the patients with recurred EV, bleeding was defined as any episode of hematemesis or melena from recurred EV or when endoscopy showed blood from EV.

4. Statistical analysis

Among the demographic and clinical parameters, continuous variables are expressed as mean and standard deviation. Differences of these variables between groups were tested with Student t-test or the Wilcoxon rank-sum test, as appropriate, after testing for normality using the Shapiro-Wilk test and for the equal variance assumption using Levene’s test. Categorical variables were expressed as frequencies and percents (%) and compared with the chi-square or Fisher exact test, as appropriate. A univariate logistic regression analysis was performed to examine the associations between the candidate predictors and the presence or absence of EV recurrence and bleeding after EVL. The odds ratio (OR) for the chance of variceal recurrence

Table 1. Patient Characteristics (n=144)

Variable		Value
Age, yr		53.8±10.4
Sex	Male	114 (79.2)
	Female	30 (20.8)
Etiology	Alcohol	62 (43.1)
	Hepatitis B	65 (45.1)
	Hepatitis C	5 (3.5)
	Others	12 (8.3)
CTP class	A	56 (38.9)
	B	67 (46.5)
	C	21 (14.6)
Splenomegaly	Absence	17 (11.8)
	Presence	127 (88.2)
Platelet, 10 ³ / μ L		85.1±46.2
Previous history of EV bleeding	Yes	85 (59.0)
	No	59 (41.0)
Endoscopic findings		
EV class	F2	105 (72.9)
	F3	39 (27.1)
Gastric varices	Absence	70 (48.6)
	Presence	74 (51.4)
EUS findings		
EV size, mm		8.7±2.5
Para-ECV size, mm		7.7±2.2
Perforating vein size, mm		3.2±0.7
Perforating vein number		3.5±0.7
Session of EVL, n		3 (3–4)
Nonselective β -blocker	Yes	115 (79.9)
	No	29 (20.1)
Recurrence of EV	Absence	102 (70.8)
	Presence	42 (29.2)
Bleeding of EV	Absence	134 (93.1)
	Presence	10 (6.9)

Data are presented as mean±SD, number (%), median (interquartile range).

CTP, Child-Turcotte-Pugh; EV, esophageal varices; EUS, endoscopic ultrasonography; ECV, esophageal collateral veins; EVL, endoscopic variceal ligation.

and variceal bleeding was calculated for each predictor. Akaike Information Criterion (AIC)-based backward selection was used to drop insignificant variables in the multivariate logistic regression.¹² The initial regression model included factors that showed the significance based on the univariate logistic regression and was further refined by the AIC-based backward selection. Multiple collinearity of continuous variables was assessed by the general variance inflation factor.¹³ After the final model was determined, the probability predicted for each subject was used as input to generate a receiver-operating characteristic (ROC) curve. The area under the ROC curve (AUC) and the 95% confidence interval (CI) of this area was computed to evaluate diagnostic ability. The diagnostic test was considered to have discriminatory potential if the lower limit of the CI for the AUC was >0.5. The best cutoff probability value for each subject to have a recurrence of EV or bleeding after EVL was determined using Youden's index.¹⁴ Sensitivity, specificity, and positive and negative predictive values of the best cutoff value were calcu-

lated. A two-tailed p-value <0.05 was considered significant. All statistical analyses were performed using SAS 9.4 for Windows (SAS Institute Inc., Cary, NC, USA) and R 3.1.2 version software (<http://cran.r-project.org/>).

RESULTS

1. Patient characteristics

Among the 248 patients, 144 were included in the analysis after excluding patients who failed to achieve eradication of EV (n=36), lost to follow-up (n=26), diagnosed or developed hepatocellular carcinoma (n=9), concomitant main portal vein thrombosis (n=7), received TIPS (n=7) or BRTO (n=3), EV bleeding history within 2 years prior to prophylactic EVL (n=6), discordant data (n=5), gastric variceal bleeding (n=3), or death from another illness (n=2). Males were predominant (114/144, 79.2%). Mean age was 53.8±10.4 years. The etiologies of liver cirrhosis were hepatitis B virus (n=65, 45.1%) and alcohol (n=62,

Table 2. Baseline Characteristics in the Recurrence and Nonrecurrence Groups

Variable	Recurrence (n=42)	Nonrecurrence (n=102)	p-value
Age, yr	53.4±9.6	53.9±10.8	0.790*
Sex			
Male	34 (81.0)	80 (78.4)	0.910 [†]
Female	8 (19.0)	22 (21.6)	
Etiology			
Alcohol	15 (35.7)	47 (46.1)	0.648 [†]
Hepatitis B	22 (52.4)	43 (42.2)	
Hepatitis C	1 (2.4)	4 (3.9)	
Others	4 (9.5)	8 (7.8)	
CTP class			
A	7 (16.7)	49 (48.0)	<0.001[†]
B	24 (57.1)	43 (42.2)	
C	11 (26.2)	10 (9.8)	
Splenomegaly (presence)	36 (85.7)	91 (89.2)	0.758
Platelet, 10 ³ /μL	87.5±43.0	84.1±47.6	0.689*
Previous history of EV bleeding (yes)	24 (57.1)	61 (59.8)	0.913 [†]
Endoscopic findings			
EV class			
F2	22 (52.4)	83 (81.4)	<0.001[†]
F3	20 (47.6)	19 (18.6)	
Gastric varices (presence)	30 (71.4)	44 (43.1)	0.004[†]
EUS findings			
EV size, mm	10.2±2.6	8.1±2.2	<0.001[*]
Para-ECV size, mm	9.1±2.5	7.1±1.8	<0.001[*]
Perforating vein size, mm	3.6±0.5	3.0±0.7	<0.001[§]
Perforating vein number	3.6±0.9	3.4±0.7	0.119*
Session of EVL, n	3 (2–4)	3 (2–3)	0.089
Nonselective β-blocker (yes)	34 (81.0)	81 (79.4)	1 [†]
Bleeding of EV (presence)	10 (23.8)	0	<0.001[§]

Data are presented as mean±SD, number (%), median (interquartile range). Variables with a p-value <0.05 are shown in bold.

CTP, Child-Turcotte-Pugh; EV, esophageal varices; EUS, endoscopic ultrasonography; ECV, esophageal collateral veins; EVL, endoscopic variceal ligation.

*Student t-test assuming equal variance between the groups; [†]Chi-square test; [‡]Fisher exact test; [§]Student t-test assuming unequal variance between the groups; ^{||}Wilcoxon rank sum test.

43.1%) followed by hepatitis C virus (n=5, 3.5%). The CTP classes were 56 (38.9%) A, 67 (46.5%) B, and 21 (14.6%) C. Eighty-five patients (59.0%) had a variceal bleeding history, and 115 (79.9%) took a nonselective β -blocker. The median number of EVL sessions to achieve complete variceal eradication was three (range, 1–6). The EV classes based on the EUM findings were F2 (n=105, 72.9%), and F3 (n=39, 27.1%), and gastric varices appeared in 74 patients (51.4%). Based on the EUM findings, the mean diameters of EV, para-ECVs, and perforating veins were 8.7 ± 2.5 , 7.7 ± 2.2 , and 3.2 ± 0.7 mm, respectively (Table 1).

2. Comparison of patients according to recurrence of EV

During the 1 year follow-up period, EV recurred in 42 patients (29.2%). The demographic and clinical data of the patients with (recurrence group) and without EV recurrence (nonrecurrence group) are presented in Table 2. The nonrecurrence group was mainly comprised of CTP class A (n=49, 48.0%), whereas the majority of the recurrence group were CTP class B (n=24, 57.1%). The CTP class of recurrence group was significantly higher than that of the nonrecurrence group ($p < 0.001$). EV class

F3 (47.6% vs 18.6%, $p < 0.001$) and presence of gastric varices (71.4% vs 43.1%, $p = 0.004$) were more commonly seen in the recurrence group than those in the nonrecurrence group. The mean diameters of EV, para-ECVs, and perforating veins in the recurrence group were significantly larger than those in the nonrecurrence group (EV, 10.2 mm vs 8.1 mm, $p < 0.001$; para-ECV, 9.1 mm vs 7.1 mm, $p < 0.001$; perforating vein, 3.6 mm vs 3.0 mm, $p < 0.001$; respectively).

3. Multivariate analysis and the predictive model for recurrence of EV

Several putative parameters were assessed in the 42 patients with recurrence and the 102 patients without to develop a predictive model for EV recurrence. EV class ($p < 0.001$), presence of gastric varices ($p = 0.002$), and CTP class ($p < 0.001$) were significant in the univariate logistic regression analysis. Among EUS findings, EV size ($p < 0.001$), para-ECV size ($p < 0.001$), and perforating vein size ($p < 0.001$) were predictive of EV recurrence (Table 3).

Factors with $p < 0.05$ in the univariate analysis were entered

Table 3. Univariate and Multivariate Analyses for Predicting Esophageal Variceal Recurrence

Variable	Univariable		Multivariable*	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age, yr	1.00 (0.96–1.03)	0.788		
Male sex (ref: female)	1.17 (0.49–3.03)	0.735		
Etiology (ref: others)				
Alcohol	0.64 (0.17–2.66)	0.509		
Hepatitis B	1.02 (0.29–4.18)	0.973		
Hepatitis C	0.50 (0.02–5.03)	0.587		
CTP class (ref: A)				
B	3.91 (1.60–10.64)	0.004	4.80 (1.49–15.43)	0.008
C	7.70 (2.47–26.01)	<0.001	13.06 (2.65–64.27)	0.002
Splenomegaly	0.73 (0.26–2.24)	0.555		
Platelet, $10^3/\mu\text{L}$	1.00 (0.99–1.01)	0.687		
Previous history of EV bleeding, n	1.12 (0.53–2.31)	0.768		
Endoscopic findings				
EV class F3 (ref: F2)	3.97 (1.82–8.81)	<0.001		
Gastric varices	3.30 (1.55–7.38)	0.002	2.47 (0.93–6.53)	0.069
EUS findings				
EV size, mm	1.45 (1.23–1.73)	<0.001	1.11 (0.88–1.4)	0.362
Para-ECV size, mm	1.61 (1.31–2.03)	<0.001	1.51 (1.17–1.96)	0.002
Perforating vein size, mm	7.16 (3.31–17.8)	<0.001	3.27 (1.11–9.65)	0.032
Perforating vein number	1.47 (0.91–2.42)	0.120		
Session of EVL, n	1.60 (0.99–2.62)	0.058		
Nonselective β -blocker	1.10 (0.46–2.87)	0.834		

p-values < 0.05 in the univariate analysis are shown in bold.

OR, odds ratio; CI, confidence interval; CTP, Child-Turcotte-Pugh; EV, esophageal varices; EUS, endoscopic ultrasonography; ECV, esophageal collateral veins; EVL, endoscopic variceal ligation.

*The intercept of the model is -10.8856 .

into the multivariate logistic regression analysis to determine the independent factors predicting EV recurrence. The significant EUS parameters in the multiple logistic regression were para-ECV size (OR, 1.51; 95% CI, 1.17 to 1.96; $p=0.002$), and perforating vein size (OR, 3.27; 95% CI, 1.11 to 9.65; $p=0.032$). CTP class were also significant (A/B: OR, 4.80; 95% CI, 1.49 to 15.43; $p=0.008$; A/C: OR, 13.06; 95% CI, 2.65 to 64.27; $p=0.002$).

To evaluate the performance of this model for predicting EV recurrence, a ROC analysis was conducted based on the predicted probabilities derived from the final model, and sensitivity, specificity and positive and negative predictive values were determined (sensitivity, 0.71; specificity, 0.89; accuracy, 0.84; positive predictive value, 0.73; negative predictive value, 0.88; AUC, 0.872; 95% CI of AUC, 0.811 to 0.934) (Table 4). The model with these parameters had moderate diagnostic ability for EV recurrence (Fig. 3A).

4. Comparison of the patients according to EV bleeding

Among the patients with EV recurrence, 10 experienced EV bleeding. The demographic and clinical parameters of patients with (bleeding group) and without EV bleeding (nonbleeding group) after EVL are presented in Table 5. Of the parameters, significant differences in para-ECV size and perforating vein

size were detected by EUS. The mean diameters of para-ECVs and perforating veins in the bleeding group were significantly greater than those in the nonbleeding group (para-ECV, 11.1 mm vs 8.5 mm, $p=0.003$; perforating vein, 3.9 mm vs 3.5 mm, $p=0.028$; respectively).

5. Multivariate analysis and development of the predictive model for EV bleeding

All parameters were tested by univariate logistic regression analysis, and para-ECV size and perforating vein size were positively correlated to EV bleeding (para-ECV: OR, 1.54; 95% CI, 1.14 to 2.23; $p=0.010$; perforating vein: OR, 5.69; 95% CI, 1.23 to 39.96; $p=0.044$; respectively) (Table 6).

In the multivariate logistic regression analysis using AIC-based backward selection to drop insignificant terms from the model, the final model included para-ECV size ($p=0.012$) and perforating vein size ($p=0.073$ by the likelihood ratio statistic). The adjusted OR for perforating vein size was 4.72 (95% CI, 0.82 to 27.07; $p=0.082$), whereas para-ECV size was positively correlated with EV bleeding (adjusted OR, 1.51; 95% CI, 1.06 to 2.16; $p=0.022$) (Table 6).

To evaluate the performance of this model for predicting EV bleeding, a ROC analysis was conducted based on the predicted probabilities derived from the final model, and sensitivity, speci-

Table 4. Diagnostic Performance of the Final Model

Model	SEN	SPE	ACC	PPV	NPV	AUC	95% CI of AUC
Nonrecurrence vs recurrence*	30/42 (0.71)	91/102 (0.89)	121/144 (0.84)	30/41 (0.73)	91/103 (0.88)	0.872 [†]	0.811–0.934
Nonbleeding vs bleeding [‡]	8/10 (0.8)	24/32 (0.75)	32/42 (0.76)	8/16 (0.5)	24/26 (0.92)	0.811 [§]	0.630–0.992

The best cutoff values were 0.4025[†] and 0.2392[§] according to Youden's method.

SEN, sensitivity; SPE, specificity; ACC, accuracy; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve; CI, confidence interval.

*The model for recurrence: $-9.18+0.45$ (gastric varices)+0.44 (para-EV [mm])+1.45 (perforating vein [mm])–1.38 (Child-Pugh class A)+0.21 (Child-Pugh class C); [†]The model for bleeding: $-10.96+0.41$ (para-EV [mm])+1.55 (perforating vein [mm]).

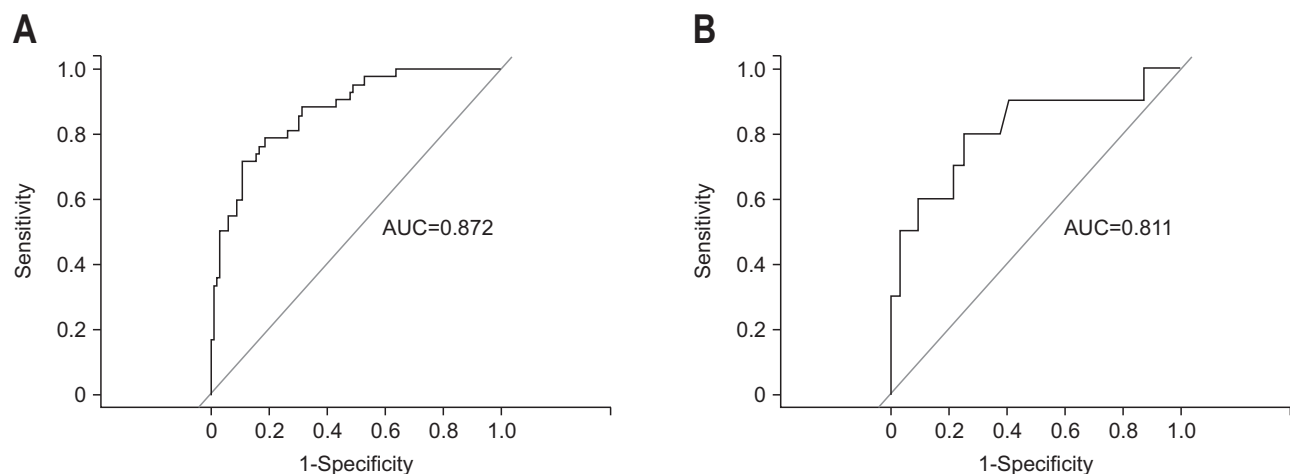


Fig. 3. Predictive model for recurrence (A) and bleeding (B) of esophageal varices after variceal obliteration. AUC, area under the curve.

Table 5. Baseline Characteristics in the Bleeding and Nonbleeding Groups

Variable		Bleeding (n=10)	Nonbleeding (n=32)	p-value	
Age, yr		52.6±8.7	53.7±9.9	0.758*	
Sex	Male	10 (100)	24 (75)	0.165 [†]	
	Female	0	8 (25)		
Etiology	Alcohol	4 (40)	11 (34.4)	0.320 [†]	
	Hepatitis B	5 (50)	17 (53.1)		
	Hepatitis C	1 (10)	0		
	Others	0	4 (12.5)		
CTP class	A	1 (10)	6 (18.8)	0.689 [†]	
	B	7 (70)	17 (53.1)		
	C	2 (20)	9 (28.1)		
Splenomegaly	Absence	0	6 (18.8)	1 [†]	
	Presence	10 (100)	26 (81.2)		
Platelet, 10 ³ /μL		74.4±33.4	91.6±45.3	0.384 [†]	
Previous history of EV bleeding	Yes	4 (40)	20 (62.5)	0.281 [†]	
	No	6 (60)	12 (37.5)		
Endoscopic findings	EV class	F2	5 (50)	1 [§]	
		F3	5 (50)		15 (46.9)
	Gastric varices	Absence	3 (30)	9 (28.1)	1 [†]
		Presence	7 (70)	23 (71.9)	
EUS findings	EV size, mm	10.5±2.7	10.1±2.6	0.668*	
	Para-ECV size, mm	11.1±2.9	8.5±2.0	0.003*	
	Perforating vein size, mm	3.9±0.4	3.5±0.5	0.028*	
	Perforating vein number	3.7±1.2	3.6±0.8	0.811*	
Session of EVL, n		3 (2–4)	3 (2–4)	0.851 [†]	
Nonselective β-blocker	Yes	8 (80)	26 (81.2)	1 [†]	
	No	2 (20)	6 (18.8)		

Data are presented as mean±SD, number (%), median (interquartile range). p-values <0.05 are shown in bold.

CTP, Child-Turcotte-Pugh; EV, esophageal varices; EUS, endoscopic ultrasonography; ECV, esophageal collateral veins; EVL, esophageal variceal ligation.

*Student t-test assuming equal variance between the groups; [†]Fisher exact test; [‡]Wilcoxon rank sum test; [§]Chi-square test.

ficity and positive and negative predictive values were determined (sensitivity, 0.80; specificity, 0.75; accuracy, 0.76; positive predictive value, 0.50; negative predictive value, 0.92; AUC, 0.811; 95% CI of AUC, 0.630 to 0.992) (Table 4). The model also had moderate diagnostic ability for EV bleeding (Fig. 3B).

DISCUSSION

Esophageal varices consist of collateral vascular structures around the esophagus.¹⁵ The development of EUS and imaging systems has made it possible to observe collateral vascular structures and evaluate the vascular networks connected to variceal columns. For EV recurrence is more frequently found during EVL than in sclerotherapy,^{16,17} the role of EUS is more salient when doing EVL.

We investigated EUM parameters to create a predictive model for EV recurrence and bleeding after EVL. The largest diameter of para-ECVs and perforating veins, and CTP class were significant factors predicting EV recurrence, and the diameter of para-ECVs was predictive of EV bleeding. The AUCs of the predictive model for EV recurrence and bleeding were 0.872 (95% CI, 0.811 to 0.934), and 0.811 (95% CI, 0.630 to 0.992) respectively. After all, EV recurrence happened again in nearly 30% of our patients. These models can predict over 80% of recurrence or bleeding before initiating EVL therapy. Carvedilol or high dose nonselective β-blocker titrated with hemodynamic parameter or HVPG if available would be preferred in those who were liable to fall into recurrence or bleeding even after eradication of varices.

Several studies have evaluated the role of EUS in predicting recurrence of the EVs following EVL. Leung *et al.*⁹ and Lo *et*

Table 6. Univariate and Multivariate Analyses of Candidate Predictors of Esophageal Variceal Bleeding

Variable	Univariable		Multivariable*	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age, yr	0.99 (0.91–1.06)	0.751		
Platelet, 10 ³ /μL	0.99 (0.97–1.01)	0.276		
CTP class (ref: A)				
B	2.47 (0.33–51.17)	0.439		
C	1.33 (0.10–32.55)	0.829		
Previous history of EV bleeding, n	2.50 (0.59–11.56)	0.217		
Endoscopic findings				
EV class F3 (ref: F2)	1.13 (0.27–4.83)	0.863		
Gastric varices	0.91 (0.20–4.95)	0.909		
EUS findings				
EV size, mm	1.06 (0.80–1.4)	0.660		
Para-ECV size, mm	1.54 (1.14–2.23)	0.010	1.51 (1.06–2.16)	0.022
Perforating vein size, mm	5.69 (1.23–39.96)	0.044	4.72 (0.82–27.07)	0.082
Perforating vein number	1.11 (0.47–2.66)	0.806		
Session of EVL, n	0.90 (0.36–2.15)	0.816		
Nonselective β-blocker	0.92 (0.17–7.14)	0.930		

p-values <0.05 in the analysis are shown in bold.

OR, odds ratio; CI, confidence interval; CTP, Child-Turcotte-Pugh; EV, esophageal varices; EUS, endoscopic ultrasonography; ECV, esophageal collateral veins; EVL, esophageal variceal ligation.

*The intercept of the model is –10.9586.

*al.*¹⁸ reported that EV recurrence and bleeding increase significantly in patients with the severe-grade para-ECVs as observed in our study. Konishi *et al.*¹⁹ showed that patients experiencing EV recurrence after EVL are more likely to have severe-grade perforating veins before treatment than those without recurrence (71.4% vs 12.5%, $p < 0.01$). Furthermore, early recurrence (≤ 3 months) of EV following EVL is closely related to the presence of severe-grade cardiac perforating veins, compared to that of mild perforating veins (90.9% vs 21%, $p < 0.01$). Masalaite *et al.*²⁰ suggested that severe peri-ECVs and multiple peri-ECVs are significant and independent prognostic factors associated with variceal recurrence risk, but not with para-ECVs or perforating veins. However, we found it very difficult to define peri-ECVs accurately because they were too small to measure (1 to 2 mm) and too numerous to count in a single patient.

Recurred EVs in our patients were newly formed beside the EVL fibrotic scars. It seemed that large diameter of para-ECVs and PVs played a role forming new collateral vessels to supply EVs after their complete obliteration. The recurrence of new EV rarely occurred when para-ECV and PV diameters were small. In addition, poor liver function as reflected by high CTP class increased the recurrence of EV. Among the patients who experienced bleeding, 84% was Child B or C, but which was low as much as 61% in all patients. This disparity can explain why CTP class was significant as a predictor in EV recurrence, yet not in EV bleeding. If we included a larger number of patients with

more advanced liver cirrhosis would be one of most important risk factors for EV bleeding as well.

The finding that para-ECV size only tended to be a significant predictor could be due to the situation where perforating veins were obliterated by band ligation, but para-ECVs were not, as they are outside of esophageal wall. Use of nonselective β-blockers and a history of EV bleeding were not associated with EV recurrence or bleeding during the follow-up period.

This study had several limitations most of which originated from the retrospective design. First, selection bias may have occurred because we did not include all the patients with significant sized EV and the study was performed in a single tertiary medical center. As a considerable number of patients failed to achieve complete eradication ($n=36$) or were lost to follow-up ($n=26$), the incidence of recurrence and bleeding may have been underestimated. Measurement bias may have been occurred when we determined who had complete eradication or recurrence of EV. Therefore, another expert who was blinded to the patient information reviewed and interpreted the results through videotape. Discordant results were excluded from the analysis. Since retrospectively collected data alcohol uptake that is likely to be a risk factor was not adjusted in the analysis. Third, our results can only be applied to the patients with cirrhosis who are stable and eligible to undertake EUS. However, our study included a large number of patients and followed up longer period as compared to previous studies. We hope that it can grow

the knowledge of the hemodynamics of esophageal vascular network. Through the EUS, physicians have a more information about who and how much not to respond to EVL. Hence, they are able to decide in advance to switch to other modality or perform EVL repeatedly on a short-term basis.

Also, a future study should focus on managing patients with large para-ECVs or perforating veins to prevent EV recurrence and bleeding after EVL. The proper follow-up period and early EVL prophylaxis for these patients will help achieve complete eradication and reduce variceal bleeding.

In summary, the largest diameter para-ECVs and perforating veins were significant risk factors for EV recurrence or bleeding after EVL. The model constructed with these EUS parameters showed good predictive ability for EV recurrence and bleeding.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Author contribution: Conceived and designed the experiments, S.W.J., H.S.K., S.G.K. Collected the data, J.Y.J., S.H.L., H.S.K. Analyzed the data, J.S.L. Contributed to validate the data, Y.S.K., B.S.K. Wrote the paper, S.W.J., H.S.K., S.G.K., J.Y.J., S.H.L., H.S.K., J.S.L., Y.S.K., B.S.K.

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