World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v17.i28.3347

World J Gastroenterol 2011 July 28; 17(28): 3347-3352
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

BRIEF ARTICLE

Risk factors for predicting early variceal rebleeding after endoscopic variceal ligation

Liang Xu, Feng Ji, Qin-Wei Xu, Mie-Qing Zhang

Liang Xu, Feng Ji, Qin-Wei Xu, Mie-Qing Zhang, Department of Gastroenterology, First Affiliated Hospital, Zhejiang University School of Medicine, 79 Qingchun Road, Hangzhou 310003, Zhejiang Province, China

Author contributions: Xu L wrote the manuscript and collected some of the data in addition to performing statistical analysis; Ji F designed the study; Xu QW co-wrote the manuscript; Zhang MQ collected most of the data.

Correspondence to: Dr. Feng Ji, Department of Gastroenterology, First Affiliated Hospital, Zhejiang University School of Medicine, 79 Qingchun Road, Hangzhou 310003, Zhejiang Province, China. jifeng1126@sina.com
Telephone: +86-571-87236568 Fax: +86-571-87236611
Received: October 19, 2010 Revised: February 26, 2011
Accepted: March 5, 2011
Published online: July 28, 2011

Abstract

AIM: To analyze the clinical risk factors for early variceal rebleeding after endoscopic variceal ligation (EVL).

METHODS: 342 cirrhotic patients with esophageal varices who received elective EVL to prevent bleeding or rebleeding at our endoscopy center between January 2005 and July 2010. were included in this study. The early rebleeding cases after EVL were confirmed by clinical signs or endoscopy. A case-control study was performed comparing the patients presenting with early rebleeding with those without this complication.

RESULTS: The incidence of early rebleeding after EVL was 7.60%, and the morbidity of rebleeding was 26.9%. Stepwise multivariate logistic regression analysis showed that four variables were independent risk factors for early rebleeding: moderate to excessive ascites [odds ratio (OR) 62.83, 95% CI: 9.39-420.56, $P < 0.001$], the number of bands placed (OR 17.36, 95% CI: 4.00-75.34, $P < 0.001$), the extent of varices (OR 15.41, 95% CI: 2.84-83.52, $P = 0.002$) and prothrombin time (PT) > 18 s (OR 11.35, 95% CI: 1.93-66.70, $P = 0.007$).

CONCLUSION: The early rebleeding rate after EVL is mainly affected by the volume of ascites, number of rubber bands used to ligate, severity of varices and prolonged PT. Effective measures for prevention and treatment should be adopted before and after EVL.

Key words: Esophageal variceal bleeding; Endoscopic variceal ligation; Loop ligature; Early rebleeding; Risk factor

Peer reviewer: Piero Marco Fisichella, MD, Assistant Professor of Surgery, Medical Director, Swallowing Center, Loyola University Medical Center, Department of Surgery, Stritch School of Medicine, 2160 South First Avenue, Room 3226, Maywood, IL 60153, United States

Xu L, Ji F, Xu QW, Zhang MQ. Risk factors for predicting early variceal rebleeding after endoscopic variceal ligation. *World J Gastroenterol* 2011; 17(28): 3347-3352 Available from: URL: http://www.wjgnet.com/1007-9327/full/v17/i28/3347.htm DOI: http://dx.doi.org/10.3748/wjg.v17.i28.3347

INTRODUCTION

Acute esophageal variceal bleeding is a severe and vital complication threatening cirrhotic patients' lives. Variceal bleeding occurs at a yearly rate of 5%-15% in cirrhotic patients. The most important predictor of bleeding is the size of varices, with the highest risk of first bleeding (15% per year) occurring in patients with large varices[1]. Other predictors of bleeding are decompensated cirrhosis (Child-Pugh B/C) and the endoscopic presence of red wale marks[1]. Trials have demonstrated that endoscopic variceal ligation (EVL) is an effective method to prevent variceal bleeding[2]. However, early recurrent bleeding after EVL (rebleeding occurring between 24 h and 14 d after the operation) is also fatal[3], and is mainly due to early spontaneous slippage of rubber bands leaving the

unhealed ulcer[4]. Only a few studies have reported the possible predictive factors for rebleeding after EVL: previous upper variceal bleeding, peptic esophagitis, a high platelet ratio index score, coagulation function, and number of varices[3,4]. Until now, there has been no general consensus on the risk factors and measures to prevent early rebleeding. The aim of this study was to assess the risk factors for early variceal rebleeding after EVL.

MATERIALS AND METHODS

Patients

Enrolled in this study were 342 inpatients who, between January 2005 and July 2010, underwent EVL at our endoscopy center for treatment of variceal bleeding due to cirrhosis. Patients who had accepted injection sclerotherapy prior to the EVL procedure were excluded. There were 242 males and 100 females, and the average age was 52.7 ± 10.9 years (range: 24-79 years). Among these 342 patients, the cause of cirrhosis in 237 cases was viral hepatitis, alcoholism was the cause in 31 cases, and the remaining 48 were due to biliary disease, schistosomiasis infection, autoimmune hepatitis or an unknown pathogenesis.

The 342 patients were divided into rebleeding and non-rebleeding groups. Observations included baseline characteristics (general features, biochemical and ultrasonic data), endoscopic details and medications after EVL (Tables 1-3). The variables were retrospectively collected in a computer database and the medical records of the hospital.

Endoscopic procedure for EVL

The endoscopic procedures followed the guidelines established by the Chinese Endoscopy Institute in 2000[5]. Briefly, selected varices (above the cardia 2-3 cm) were visualized and aspirated into the banding chamber of the ligator. Suction was maintained until the screen became red, and then the band was deployed by rotating the handle clockwise until the band release was felt. The bands were then launched onto varices in ascending order through the esophagus. The devices used were either an Olympus XQ 240 or 260 endoscope, and a 6- or 10-shooter Saeed multi-band ligator (Wilson-Cook Medical).

Follow-up

Following EVL, standard doses of proton pump inhibitors (PPIs) were administered for 2 wk for most patients. Food intake was allowed 24 h after the procedure in cases of prophylactic EVL, and at the discretion of the physician in cases of emergent EVL for acute bleeding. Early rebleeding after EVL was defined as: (1) recurrent hematemesis, and/or melena, and/or bloody fluid drained by nasogastric tube, occurring between 24 h and 14 d after the operation; or (2) a decrease in hemoglobin by at least 20 g/L, or a transfusion of more than 2 units of concentrated RBC needed within 24 h, or hypovolemic shock occurs[3].

In all rebleeding patients, somatostatin (0.25 mg/h) and PPI infusion (omeprazole 40-80 mg/d) were given until active bleeding stopped. Twelve patients received an esophageal balloon tamponade. Endoscopic sclerotherapy injections were performed in 5 patients, and 1 patient had emergency devascularization surgery.

Statistical analysis

Continuous variables were stated as mean ± SD, and Student's *t*-test was used to assess the difference between those variables. Bivariate associations between categorical variables were analyzed by Pearson's χ^2 test or Fisher's exact test. Initially, each risk factor was examined independently, which produced the unadjusted odds ratio (OR) and 95% CI. We then selected the significant candidate variables (hemoglobin, bilirubin, prothrombin time (PT), albumin and portal vein diameter were dichotomized) identified by univariate analysis to undergo binary logistic regression analysis (forward stepwise) to determine the independent risk factors for rebleeding after EVL. Two-sided *P*-values < 0.05 were considered statistically significant. We used SPSS 17 software for all statistical analyses.

All data were managed anonymously. The local ethics committee confirmed that no ethical approval was needed for this study.

RESULTS

Outcome

Among the 342 patients treated with EVL, 26 patients (7.60%) developed early rebleeding. The rebleeding occurred with a mean delay of 8.0 ± 2.3 d (range: 3-13 d). Of these, 21 patients (80.8%) rebled between the 7th and 13th day after EVL, overwhelmingly more than those that rebled within the first 7 d. All of the rebleeding cases were caused by esophageal variceal bleeding, which were confirmed by endoscopy or clinical manifestations. Seven patients (26.9%) died despite positive rescue. We failed to find any benefit in the use of PPIs, somatostatin, β-blockers or sucralfate for the prevention of early rebleeding after EVL.

Baseline characteristics

The characteristics of both the rebleeding and non-rebleeding groups are presented in Table 1. The mean age of the patients who rebled was 57.5 ± 8.3 years, as compared with 52.3 ± 11.0 years for those who did not rebleed ($P = 0.02$). Patients who had had splenectomy or devascularization procedures prior to EVL were more likely to rebleed after EVL ($P < 0.01$). The rebleeding patients had worse Child-Pugh scores (class A, $n = 3.8\%$, class B, $n = 23.1\%$, class C, $n = 73.1\%$) compared with the controls (class A, $n = 39.6\%$, class B, $n = 54.7\%$, class C, $n = 5.7\%$, $P < 0.01$). For the indices scored in the Child-Pugh classification, encephalopathy, ascites, albumin, bilirubin and PT, all were significantly different between the two groups: the *P*-values were < 0.01,

Table 1 Univariate analysis for baseline characteristics

Variable	Non-rebleeding (n = 316)	Rebleeding (n = 26)	P-value	OR	95% CI
Male/female	227/89	15/11	0.13		
Age (yr)	52.3 ± 11.0	57.5 ± 8.3	0.02		
Etiology of cirrhosis					
Virus	237	21	0.60		
Alcohol	31	1			
Others	48	4			
Comorbidities					
Diabetes	35	5	0.21		
Liver cancer	19	2	0.67		
History of surgery					
Splenectomy or devascularization	100	16	< 0.01	3.08	1.38-6.88
Liver cancer surgery	8	0	1		
Liver transplantation	3	0	1		
Child-Pugh score					
A	125	1	< 0.01		
B	173	6			
C	18	19			
Encephalopathy	8	10	< 0.01	24.06	8.36-69.23
Blood loss before EVL (mL)	736 ± 418	1854 ± 657	< 0.01		
Ascites					
None/mild	285	6	< 0.01	26.18	10.25-66.82
Moderate/excessive	31	20			
Portal vein diameter (mm)	12.9 ± 2.1	15.9 ± 2.2	< 0.01		
Portal vein diameter ≥ 14 mm	113	24	< 0.01	21.56	5.00-92.89
Portal vein thrombosis	37	13	< 0.01	7.54	3.25-17.50
Hemoglobin (g/L)	97.0 ± 20.8	71.8 ± 13.2	< 0.01		
Hemoglobin < 90 g/L	112	24	< 0.01	21.86	5.07-94.19
Platelets (10^9/L)	121 ± 77	96 ± 99	0.118		
Albumin (g/L)	35.2 ± 5.6	29.2 ± 4.2	< 0.01		
Albumin < 28 g/L	32	8	< 0.01	3.94	1.59-9.79
ALT (U/L)	32.4 ± 22.2	36.0 ± 18.4	0.42		
AKP (U/L)	108.3 ± 200.1	142.8 ± 96.5	0.39		
Bilirubin (μmol/L)	21.4 ± 13.4	27.7 ± 14.9	0.02		
Bilirubin > 34 μmol/L	34	9	< 0.01	4.39	1.82-10.62
PT (s)	15.7 ± 2.4	20.1 ± 3.5	< 0.01		
PT > 18 s	43	20	< 0.01	19.07	7.21-45.30

EVL: Endoscopic variceal ligation; ALT: Alanine aminotransferase; AKP: Alkaline phosphatase; PT: Prothrombin time; OR: Odds ratio.

Table 2 Univariate analysis for endoscopic data

Variable	Non-rebleeding (n = 316)	Rebleeding (n = 26)	P-value	Odds ratio	95% CI
Esophageal varices grade					
Mild	11	0	< 0.01		
Moderate	179	0			
Severe	126	26			
Number of varies	3.2 ± 0.8	4.5 ± 0.6	< 0.01		
Extent of esophageal varies					
Middle and lower section	281	4	< 0.01	44.16	14.38-135.58
Whole	35	22			
Red sign	267	26	0.04		
Gastric varies	91	25	< 0.01	61.81	8.25-462.97
Portal hypertensive gastropathy	85	23	< 0.01	20.84	6.10-71.18
Number of rubber bands	5.1 ± 0.9	6.5 ± 0.5	< 0.01	22.00	6.46-74.96

< 0.01, < 0.01, 0.02 and < 0.01, respectively. Rebleeding was also associated with more blood loss before EVL (P < 0.01), increased portal vein diameter (P < 0.01), portal vein thrombosis (PVT, P < 0.01) and low hemoglobin (P < 0.01). Gender, etiology of cirrhosis, comorbidities, liver cancer surgery, liver transplantation, platelets, alanine aminotransferase and alkaline phosphatase were not significantly associated with early rebleeding.

Comparison of endoscopic data between the cases and controls

All the patients who rebled had varices classified as "se-

Table 3 Medication after endoscopic variceal ligation

Medication	Non-rebleeding (n = 316)	Rebleeding (n = 26)	P
Proton pump inhibitor	305	26	1
Somatostatin/octreotide	203	26	< 0.01
β-blocker	34	2	1
Sucralfate	176	20	0.04

Table 4 Multivariate analysis

Risk factor	P-value	OR	95% CI
Ascites (moderate to excessive)	< 0.001	62.83	9.39-420.56
Number of rubber bands	< 0.001	17.36	4.00-75.34
Extent of esophageal varies	0.002	15.41	2.84-83.52
Prothrombin time > 18 s	0.007	11.35	1.93-66.70

OR: Odds ratio.

vere", while only 40% of the controls did ($P < 0.01$). The percentage of patients with varices throughout the whole extent of the esophagus in the rebleeding group was 85%, which was nearly 8 times more than that of the controls ($P < 0.01$). The number of rubber bands placed in the rebleeding patients (6.5 ± 0.5) was greater than that of the controls (5.1 ± 0.9, $P < 0.01$). Significant differences between the two groups were also seen for number of varices ($P < 0.01$), gastric varices ($P < 0.01$), portal hypertensive gastropathy ($P < 0.01$) and red signs ($P = 0.04$).

Multivariate analysis

The significant candidate variables were selected for forward stepwise logistic regression analysis to find the independent risk factors for early rebleeding after EVL (Table 4). Four variables were identified: moderate to excessive ascites (OR 62.83, 95% CI: 9.39-420.56, $P < 0.001$), the number of bands placed (OR 17.36, 95% CI: 4.00-75.34, $P < 0.001$), the extent of varices (OR 15.41, 95% CI: 2.84-83.52, $P = 0.002$) and PT > 18 s (OR 11.35, 95% CI: 1.93-66.70, $P = 0.007$).

DISCUSSION

EVL is an effective method to prevent variceal bleeding primarily and secondarily. However, early recurrent bleeding as a vital complication after EVL has not been studied fully. There are only a few studies reporting the possible predictors for early rebleeding after EVL, and the sample sizes are usually too small[4,6]. The large sample size of our study enabled us to find the incidence, predilection time and risk factors for early rebleeding after EVL more credible. Furthermore, the emergency EVL is often supposed to be different from the elective one because of the different patient conditions and technical difficulty. We just focused on the rebleeding risk in prophylactic EVL operations rather than in emergency ones, not as the earlier study[4].

A prior study[7] reported that the rate of early rebleeding following EVL was between 9% and 19%, which is close to our result (7.6%). We also found that post-EVL bleeding was most likely to occur between the 7th and 13th day following the procedure. Vanbiervliet *et al*[4] reported that cases of severe bleeding after EVL were all caused by early slippage of the rubber bands, leaving the unhealed ulcus. Usually, the bands slip spontaneously within the second week after EVL, which can explain the timing of post-EVL rebleeding found in this study. On the basis of the above result, recommending a soft diet and avoiding strenuous exercise is helpful in preventing early slippage, an occurrence which can lead to life-threatening rebleeding.

In this study, we collected more expanded indices than former studies to evaluate patients with esophageal varices more comprehensively, which allowed us to draw convincing conclusions. For example, we took account of extent of varices, number of varices, portal vein diameter, PVT, history of related surgery and so on. As the result showed, there were significant differences between the cases and controls for many characteristics, such as age, surgery history, liver function, severity of varices, number of rubber bands, and so forth. But as demonstrated by the multivariate analysis, there were only four independent risk factors among these, namely moderate to excessive ascites, number of rubber bands placed, extent of varices and PT > 18 s. These four risk factors may therefore be more meaningful than the others for predicting the occurrence of early rebleeding following EVL.

Lee *et al*[8] believed that the more rubber bands that were used to ligate, the greater the possibility of rebleeding, because of the increasing ulcera. In our study, we also found that the number of rubber bands was an independent risk factor for bleeding after EVL. Therefore, for varices which were in the mild to moderate class, it may not be reasonable to launch many rubber bands. For severe varices, however, it's usually unavoidable to use more bands.

The prognosis does not only depend on the EVL procedure, but also relates to the severity of liver damage and bleeding. Yang *et al*[9] found that the Child-Pugh score for liver function was an independent risk factor of post-EVL rebleeding. Berreta *et al*[10] proved that Child-Pugh C was an independent risk factor of death from rebleeding. Our study showed that there was a difference in Child-Pugh score between the rebleeding and non-rebleeding groups. Furthermore, we revealed that ascites and PT, two of the indices for Child-Pugh classification, were independent risk factors for rebleeding after EVL, but the other three indices were not.

Ascites as an independent risk factor for early rebleeding after EVL was not reported in the study of Vanbiervliet *et al*[4]. However, they did not quantify the volume of ascites. We demonstrated that a moderate to excessive volume of ascites was the most dangerous factor predicting post-EVL bleeding (OR 62.83, 95% CI: 9.39-420.56). This may be explained by the elevated portal vein pressure that results from a larger volume of ascites. It was reported in

a previous study[11] that variceal bleeding recurred more in patients with higher basal portal vein pressure, and led to higher mortality. High portal vein pressure, therefore, is crucial for the recurrence of variceal bleeding.

Patients with decompensated cirrhosis often have coagulation disorders. One study[12] showed that an international normalized ratio > 2.3 was a predictor of death within the first 6 wk after patients were treated for their first variceal bleeding. The coagulation index as an independent predictive factor for rebleeding after EVL was reported in some previous studies[3,4], but not in another[13]. Our study showed that PT > 18 s was an independent risk factor of post-EVL bleeding (OR 11.35, 95% CI: 1.93-66.70). It is understandable that the ulcera caused by rubber bands can not heal well without normal coagulation. The prolongation of PT suggests a lack of coagulation factors Ⅰ, Ⅱ, Ⅶ or Ⅹ, or fibrinolysis acceleration. Therefore, for patients with quite prolonged PT, supplementing vitamin K1 and coagulation factors are necessary before EVL. Coagulation disorders in cirrhosis often accompany unusual thrombosis as well. There was a difference in PVT between the rebleeding and non-rebleeding groups, as stated in this study. Kayacetin *et al*[14] considered that slow blood flow in the portal vein was associated with liver damage. When liver function was poor, the blood flow through the portal vein slowed down, raising the likelihood of variceal rebleeding. Recent research reported that PVT without liver cirrhosis caused a low variceal bleeding rate[15], while the rate went up significantly once the cirrhosis presented[16]. Those findings suggest that the primary liver disease may be the dominant factor for variceal bleeding and the prognosis of cirrhosis patients with PVT depends on the severity of liver disease.

We found the other independent risk factor was the extent of varices, which also reflects the severity of varices. Varices that extend along the entire esophagus are much more dangerous than varices that are limited to the middle and lower part. On the other hand, a greater extent of varices often means that more rubber bands are needed, increasing the possibility of rebleeding.

When considering the healing of post-EVL ulcera, the use of PPIs has been reported useful in comparison with a placebo, but the effect on preventing bleeding was not conclusive[17]. In our study, almost every patient received a standard dose of PPIs for 2 wk after EVL, but there was no significant difference between the two groups. We also failed to find any benefit in the use of sucralfate for the prevention of bleeding related to post-banding ulcera. Somatostatin is helpful to reduce portal vein pressure, but it was usually only used for 3 d after EVL. We did not find that it had any preventative effect on rebleeding, which usually occurred 7-14 d after EVL. β-blocker is another useful drug to reduce portal vein pressure, and it can be taken for a long time. Disappointingly, we failed to see any benefit from it too. But the number of treated patients was very small and may not accurately reflect the facts.

A limitation of our study was that relatively few rebleeding cases occurred, which might affect the statistical analysis because of the unbalanced sample size ratio of case to control. It is expected that more samples will be collected from multiple centers in the future. Additionally, the rebleeding cases were not all confirmed by endoscopy (although clinical signs were frequently enough to confirm the source of bleeding in these cirrhosis patients), which precluded us from performing a more detailed analysis.

In conclusion, this large sample size case-control study revealed four risk factors for predicting early post-EVL rebleeding. Part of the result was accordance with some former studies, but the other part was not reported before, such as ascites and the extent of varices. So it provided doctors with some new warnings which should be paid attention to. Patients should be assessed thoroughly according to the risk factors (especially the independent ones) before EVL to minimize rebleeding. Patients with poor liver function, especially those with large ascites and coagulation disorders, should be treated positively before EVL. Improving coagulation function by supplementing vitamin K1 and coagulation factors, reducing ascites by diuretics and albumin are all expected to effectively decrease the rebleeding rate after EVL.

COMMENTS

Background

Acute esophageal variceal bleeding is a severe and vital complication threatening cirrhotic patients' lives. Trials have demonstrated that endoscopic variceal ligation (EVL) is an effective method to prevent esophageal variceal bleeding with fewer complications. However, as a rare complication, early recurrent bleeding after EVL is also fatal. There has been no general consensus on the risk factors of early rebleeding after EVL and measures to prevent this complication.

Research frontiers

Early rebleeding following EVL is mainly due to early spontaneous slippage of rubber bands leaving the unhealed ulcer. Only a few small sample studies have reported the possible predictive factors for the rebleeding. It may be related to not only the EVL procedure, but also the severity of varices and liver damage.

Innovations and breakthroughs

The large sample size of our study enabled us to find the incidence, predilection time and risk factors for early rebleeding after prophylactic EVL. We collected more expanded indices than former studies to elevate patients with esophageal varices more comprehensively, which allowed us to draw convincing conclusions. The four independent risk factors found in our study: moderate to excessive ascites, the number of bands placed, the extent of varices and prolonged prothrombin time, some of which were determined for the first time, are helpful for doctors to predict the risk after EVL.

Applications

The result has actual application values for increasing the safety of EVL. Those independent risk factors found in our study may help doctors to assess patients before EVL better and choose a more suitable time to perform the prophylactic procedure. Correcting as many risk factors as possible with effective treatment is expected to prevent the occurrence of early rebleeding after EVL.

Terminology

EVL is a method to treat esophageal varices endoscopically with fewer complications. EVL works by capturing all or part of a varix with a band ligator resulting in occlusion from thrombosis. The tissue then necroses and sloughs off in a few days to weeks, leaving a superficial mucosal ulceration, which rapidly heals.

Peer review

There are good merits of this study, mainly the very large sample size, which allows the researchers to draw strong conclusions.

REFERENCES

1 **Garcia-Tsao G**, Sanyal AJ, Grace ND, Carey W. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology* 2007; **46**: 922-938
2 **Khuroo MS**, Khuroo NS, Farahat KL, Khuroo YS, Sofi AA, Dahab ST. Meta-analysis: endoscopic variceal ligation for primary prophylaxis of oesophageal variceal bleeding. *Aliment Pharmacol Ther* 2005; **21**: 347-361
3 **Li P**, Zhang ST, Yu ZL, Yu YZ, Ji M, Yu L, Li L, Yan P, Liu YP, Pan JD. Analysis of the risk factors in early rebleeding after endoscopic variceal ligation. *Zhonghua Xiaohua Neijing Zazhi* 2006; **23**: 23-26
4 **Vanbiervliet G**, Giudicelli-Bornard S, Piche T, Berthier F, Gelsi E, Filippi J, Anty R, Arab K, Huet PM, Hebuterne X, Tran A. Predictive factors of bleeding related to post-banding ulcer following endoscopic variceal ligation in cirrhotic patients: a case-control study. *Aliment Pharmacol Ther* 2010; **32**: 225-232
5 **Committee of esophageal varicosity**, Society of Digestive Endoscopy of Chinese Medical Association. Trial scheme of diagnosing and treating gastroesophageal varices under endoscopy. *Zhonghua Xiaohua Neijing Zazhi* 2000; **17**: 198
6 **Van Vlierberghe H**, De Vos M, Hautekeete M, Elewaut A. Severe bleeding following endoscopic variceal ligation: should EVL be avoided in Child C patients? *Acta Gastroenterol Belg* 1999; **62**: 175-177
7 **Lo GH**, Chen WC, Chen MH, Lin CP, Lo CC, Hsu PI, Cheng JS, Lai KH. Endoscopic ligation vs. nadolol in the prevention of first variceal bleeding in patients with cirrhosis. *Gastrointest Endosc* 2004; **59**: 333-338
8 **Lee SW**, Lee TY, Chang CS. Independent factors associated with recurrent bleeding in cirrhotic patients with esophageal variceal hemorrhage. *Dig Dis Sci* 2009; **54**: 1128-1134
9 **Yang MT**, Chen HS, Lee HC, Lin CL. Risk factors and survival of early bleeding after esophageal variceal ligation. *Hepatogastroenterology* 2007; **54**: 1705-1709
10 **Berreta J**, Kociak D, Corti R, Morales G, Ortiz M, Laplacette M, Bellido F, Romero G, Salgado P, Tumilasci O. [Predictors of intrahospitalary mortality in the upper gastrointestinal variceal bleeding due to chronic liver disease treated endoscopically]. *Acta Gastroenterol Latinoam* 2008; **38**: 43-50
11 **Moitinho E**, Escorsell A, Bandi JC, Salmerón JM, García-Pagán JC, Rodés J, Bosch J. Prognostic value of early measurements of portal pressure in acute variceal bleeding. *Gastroenterology* 1999; **117**: 626-631
12 **Krige JE**, Kotze UK, Distiller G, Shaw JM, Bornman PC. Predictive factors for rebleeding and death in alcoholic cirrhotic patients with acute variceal bleeding: a multivariate analysis. *World J Surg* 2009; **33**: 2127-2135
13 **Vieira da Rocha EC**, D'Amico EA, Caldwell SH, Flores da Rocha TR, Soares E Silva CS, Dos Santos Bomfim V, Felga G, Barbosa WF, Kassab F, Polli DA, Carrilho FJ, Farias AQ. A prospective study of conventional and expanded coagulation indices in predicting ulcer bleeding after variceal band ligation. *Clin Gastroenterol Hepatol* 2009; **7**: 988-993
14 **Kayacetin E**, Efe D, Doğan C. Portal and splenic hemodynamics in cirrhotic patients: relationship between esophageal variceal bleeding and the severity of hepatic failure. *J Gastroenterol* 2004; **39**: 661-667
15 **Janssen HL**, Wijnhoud A, Haagsma EB, van Uum SH, van Nieuwkerk CM, Adang RP, Chamuleau RA, van Hattum J, Vleggaar FP, Hansen BE, Rosendaal FR, van Hoek B. Extrahepatic portal vein thrombosis: aetiology and determinants of survival. *Gut* 2001; **49**: 720-724
16 **de Franchis R**, Primignani M. Natural history of portal hypertension in patients with cirrhosis. *Clin Liver Dis* 2001; **5**: 645-663
17 **Boo GB**, Oh JC, Lee BJ, Lee DM, Kim YD, Park CG, Kim MW. [The effect of proton pump inhibitor on healing of post-esophageal variceal ligation ulcers]. *Korean J Gastroenterol* 2008; **51**: 232-240

S- Editor Sun H **L- Editor** O'Neill M **E- Editor** Zheng XM