Risk factors for predicting early variceal rebleeding after endoscopic variceal ligation

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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.

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

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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[3]. 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\(^\text{a}\). 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\(^\text{b, c}\). 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\(^\text{d}\). 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\(^\text{d}\).

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 \(\chi^2\) 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, \(\beta\)-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 rebled (\(P = 0.02\)). 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,
Rebleeding was also associated with more blood loss before EVL (\(< 0.01\)), increased portal vein diameter (\(< 0.01\)), portal vein thrombosis (PVT, \(< 0.01\)) and low hemoglobin (\(< 0.01\)). 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-
phylactic EVL operations rather than in emergency ones, difficulty. We just focused on the rebleeding risk in pro
is often supposed to be different from the elective one
EVL more credible. Furthermore, the emergency EVL

dilection time and risk factors for early rebleeding after
the sample sizes are usually too small
possible predictors for early rebleeding after EVL, and
studied fully. There are only a few studies reporting the
bleeding as a vital complication after EVL has not been

DISCUSSION
EVL is an effective method to prevent variceal bleed-
ing primarily and secondarily. However, early recur-
ted 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\cite{4,6}. The large sample
size of our study enabled us to find the incidence, pre-
dilection 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 pro-
phylactic EVL operations rather than in emergency ones,
not as the earlier study\cite{4}.
A prior study\cite{7} reported that the rate of early rebleed-

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.

Multivariate analysis
The significant candidate variables were selected for for-
ward stepwise logistic regression analysis to find the inde-
dependent risk factors for early rebleeding after EVL (Table 4).
Four variables were identified: moderate to excessive
ascites (OR 62.83, 95% CI: 9.39-420.5, P < 0.001), the number of rubber 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).

We just focused on the rebleeding risk in pro-
phylactic EVL operations rather than in emergency ones,
not as the earlier study\cite{4}.
A prior study\cite{7} reported that the rate of early rebleed-
ing 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\cite{5}
reported that cases of severe bleeding after EVL were
all caused by early slippage of the rubber bands, leaving
the unhealed ulcer. 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 prevent-
ing 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 occur-
rence of early rebleeding following EVL.
Lee et al\cite{8} believed that the more rubber bands that
were used to ligate, the greater the possibility of rebleed-
ing, because of the increasing ulcer. In our study, we also
found that the number of rubber bands was an indepen-
dent 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 se-
vere 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\cite{9} found that the Child-Pugh score
for liver function was an independent risk factor of post-
EVL rebleeding. Berreta et al\cite{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 in-
dependent risk factors for rebleeding after EVL, but the
other three indices were not.

Ascites as an independent risk factor for early rebleed-
ing after EVL was not reported in the study of Vanbiervliet
et al\cite{5}. 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

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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  |

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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 differ-
ces between the two groups were also seen for number of
varices (P < 0.01), gastric varices (P < 0.01), portal hy-
pertensive gastropathy (P < 0.01) and red signs (P = 0.04).
a previous study concluded that variceal bleeding occurred 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 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, but not in another. 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 ulcer caused by rubber bands cannot 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. 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, while the rate went up significantly once the cirrhosis presented. 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 ulcers, the use of PPIs has been reported useful in comparison with a placebo, but the effect on preventing bleeding was not conclusive. 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-bandung ulcers. 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. -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 re-bleeding 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.
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