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Research Article

Incidence and risk factors contributing for early variceal rebleeding after esophageal variceal ligation (EVL)

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Abstract: Our aim is to assess incidence & risk factors contributing for early variceal rebleeding after esophageal variceal ligation (EVL). A prospective study was conducted on eighty patients with chronic liver diseases who underwent EVL. Follow up of patients for 2 weeks was done to evaluate the outcome then patients were divided into non-rebleeding group including 71 patients and early variceal rebleeding group including 9 patients. All patients were subjected to full history and clinical assessment, routine laboratory investigations, Child-Pugh classification, MELD score, abdominal ultrasonography, upper endoscopy to assess esophageal varices grade, number, extent, gastic varices, severity of portal hypertensive gastropathy and number of rubber bands used. Our results revealed incidence of early variceal rebleeding following EVL of 11%. Low serum albumin, high serum Creatinine, BUN, WBC and total bilirubin were risk factors contributing for early variceal rebleeding after EVL. Gastric varices, esophageal varices grade and extent are endoscopic risk factors contributing for early variceal rebleeding after EVL. The presence of ascites, history of multiple number of sessions of previous intervention, higher MELD score and Child-Pugh class C were statistically significant (p<0.05) in the rebleeding group compared to non rebleeding. Early variceal rebleeding following EVL was detected in 11% of our patients. Poor liver function as indicated by Child-Pugh and MELD scores with endoscopic findings of higher esophageal varices grade, number and extent of esophageal varices, Presence of gastric varices and number of session of previous intervention were risk factors contributing for early variceal rebleeding after EVL.
Keywords: Esophageal varices, esophageal variceal ligation (EVL),Early variceal rebleeding.

INTRODUCTION

Bleeding esophageal varices represent one of the most common causes of mortality among patients with chronic liver disease. The incidence of varices in cirrhotic patients is approximately 60-80%. The risk of bleeding may reach 25-35 % of all cases within the first year of variceal detection. The mortality from each episode of variceal bleeding is 17-57 % [1].

Within the first two years of detection of varices, the incidence of the first attack of bleeding ranges from 20-40 % of all cases, whereas the incidence of recurrent bleeding is 30-40 % within the following 2 to 3 days and 60 % within one week. Therefore, prevention of esophageal variceal bleeding remains the cornerstone of long-term management of patients with liver cirrhosis [2].

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. Other predictors of bleeding are decompensated cirrhosis (Child-Pugh B/C) and the endoscopic presence of red wale marks [3].

Early rebleeding after EVL (rebleeding occurring between 24 h and 14 d after the operation) is also fatal [4], and is mainly due to early spontaneous slippage of rubber bands leaving the unhealed ulcer [5]. Only a few studies have reported the possible predictive factors for early rebleeding after EVL: previous variceal bleeding, peptic esophagitis, a high platelet ratio index score, coagulation function, and number of varices [5].

The aim from this study is to assess incidence & risk factors contributing for early variceal rebleeding after esophageal variceal ligation (EVL) whether done as prophylactic or therapeutic.

PATIENTS AND METHODS

Study group:

This work was accomplished at Ain Shams University hospital and Theodor Bilharz Research Institute (TBRI), in the period from the first of April 2012 till the 30th of June 2013 where eighty patients with chronic liver disease underwent EVL were studied. According to occurrence of early variceal rebleeding after EVL (bleeding occurring between 24 h and 14 d after the operation), the patients were classified into 2 groups.

Group (1): non-rebleeding after EVL including (71) patients.

Group (2): early variceal rebleeding after EVL including (9) patients.

Inclusion criteria

All patients with liver cirrhosis who underwent EVL whether done as prophylactic or therapeutic.

Exclusion criteria:

Patients with HCC or who refused participation in the study.

Methodology

All participants in the study were subjected to the following:

- Full medical history: Stressing on number of session of previous intervention.
- Full Clinical examination.
- Laboratory investigations including: Complete blood count, liver Function Tests {Aspartate aminotransferase (AST), alanine aminotransferase (ALT), total and direct serum bilirubin, total protein and serum albumin by standard laboratory tests}, renal Function Tests: serum creatinine and blood urea nitrogen (BUN), coagulation profile: prothrombin time (PT), prothrombin concentration (PC) and international normalized ratio (INR) by standard lab tests.
- Abdominal Ultrasonography using Hitachi, EUB-5500 with stress comment on liver echogenicity (bright or coarse echo pattern) and criteria suggestive of chronic liver disease and cirrhosis, ascites (absent, mild, moderate or marked ascites [6], portal vein diameter and patency and size of spleen.
- Child-Pugh score-classification: [7].
- MELD score was calculated for all patients. According to the formula score = [9.57 x log creatinine (mg/dl) + 3.78 x log bilirubin (mg/dl) +11.2 x log INR +6.4] which is done on MELD score web site on internet [8].
- Upper endoscopy: Using Pentax EG 2940 scope for

  - grading and banding the oesophageal varices following the guidelines established by the Chinese Endoscopy Institute in 2000 [9].

Grade I: Varices at the level of mucosa.

Grade II: Varices smaller than 5 mm & fulfilling less than 1/3 of the esophageal lumen.

Grade III: Varices larger than 5 mm & fulfilling more than 1/3 of the esophageal lumen.

Grade IV: Varices occupying more than 2/3 of esophageal lumen [10].

  - Esophageal varices number and Extent: Middle, lower section or whole oesophagus.
  - Red sign.
  - Gastric varies.
  - Number of rubber bands applied.
  - Severity of Portal hypertensive gastropathy.
- Following EVL, all patients were given standard doses of proton pump inhibitors (PPIs) for 2 wk. Early rebleeding after EVL will be defined as: (1) 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 haemoglobin by at least 2 g/L, or a transfusion of more than 2 units of concentrated RBC needed within 24 h, or hypovolemic shock occurs.
- Informed consent from all patient in study.

Statistical Analysis:

IBM SPSS statistics (V. 20.0, IBM Corp., USA) was used for data analysis. Data were expressed as Mean ± SE and were compared using Fisher's exact test to study the association between each two variables for categorical variables and Mann-Whitney tests. Statistical significance was defined as a p value less than <0.05. Statistical analysis was performed using Graph pad prism for windows (release 6.0).

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the local hospital ethics committees for human investigations.

RESULTS

A cohort of 80 patients with chronic liver diseases were enrolled in this study after EVL of their esophageal varices whether done as prophylactic or therapeutic. According to occurrence of early rebleeding after EVL, the patients were classified into 2 groups. Group (1) non rebleeding group including 71 patients and Group (2) with early variceal rebleeding after EVL including 9 patients. Demographic data of the studied groups are shown in Table (1). Age was ranging from 28 up to 83 years in group (1) with mean age ±SE (37.15±1.71); 48 (67.6%) patients were males and 23 (32.4%) were females. In group (2), age was ranging from 50 up to 63 years with mean age ±SE was (41.8±0.92); seven (68.8%) patients were males and 2 (31.3%) patients were females.

Haematological and biochemical characteristics of the two studied groups are shown in

Table (2). There is significant increase in WBC (p<0.05), total bilirubin (p<0.01), serum Creatinine (p<0.05), BUN (p<0.05) in the rebleeding group compared to non rebleeding. Serum albumin shows significant decrease (p<0.05) in the rebleeding group compared to non rebleeding. Comparison between the two groups regarding ultrasonographic finding are shown in Table (3). No significant differences were found between the two groups regarding portal vein diameter, Portal vein thrombosis and size of spleen. Ascites was found significant (p<0.01) in the rebleeding group compared to non rebleeding (Figure.1).

Table (4) and (Figure.2) shows comparison between the two groups regarding Child-Pugh classification and MELD scores. Child-Pugh class C is significant (p<0.05) in the rebleeding group compared to non rebleeding. Also statistically significant (p<0.01) higher MELD scores was found in the rebleeding group compared to non rebleeding.

Comparison of endoscopic findings of the studied groups are shown in Table (5). Higher grades of esophageal varices (grade IV) was found with significant (p<0.01) in the rebleeding group compared to non rebleeding. Regarding to extent of esophageal varices (Figure 3); in group (1), 28 patients (39.4%) had lower 1/3 esophageal varices, 23 (32.4%) had lower 1/2 esophageal varices and 20 (28.2%) had lower 2/3 esophageal varices. In group (2), 2 patients (22.2%) had lower 1/3 esophageal varices, none of patients had lower 1/2 esophageal varices and 7 patients (77.8%) had lower 2/3 esophageal varices. These data showed significant difference (p<0.01) in the rebleeding group compared to non rebleeding. Also the number esophageal varices was found significant (p<0.05) in the rebleeding group compared to non rebleeding. Red sign showed no significant difference between the two groups. Gastric varices was found significant (p<0.05) in the rebleeding group compared to non rebleeding. Portal hypertensive gastropathy showed no significant difference between the two groups. Regarding the number of rubber bands, the Mean ± SE was (4.183±0.78) for group (1) versus (4.66±0.60) for group (2) with no significant difference between the two groups. The number of session of previous intervention showed highly significant differences (p<0.01) in the rebleeding group compared to the non rebleeding.

Table-1: Demographic data of the studied groups

	non rebleeding after EVL (n= 71)	rebleeding after EVL (n= 9)
Age (yrs.) mean±SE	28-83 37.15±1.71	50-63 41.8±0.92
Sex Female/Male	23/48 (32.4/67.6%)	2/7 (31.3/68.8%)

Table-2: Haematological and biochemical characteristics of the studied groups.

	non rebleeding after EVL (n= 71)	rebleeding after EVL (n= 9)
HB	9.67±0.25	8.83±0.58
WBC	7.41±0.63	9.46 ± 1.22*
Platelet count	103.08±8.39	96.77±23.36
ALT(U/L)	67.47±4.29	36.33±9.35
AST(U/L)	41.12±3.05	77.44±26.32
D.BIL (mg/dl)	2.88±0.32	7.63±3.02*
T.BIL (mg/dl)	1.5±0.09	4.34±1.74**
TP (g/dL)	6.72±0.05	5.88±0.38
ALB (g/dl)	2.47±0.05	2.07±0.14[a]
Creatinine(mg/dL)	1.02±0.07	1.56±0.28*
BUN (mg/dl)	25±2.12	44.66±9.26*
PT(second)	16.32±0.47	17.93±1.54
PC(second)	58.2±1.90	52.18±5.56
INR	1.48±0.04	1.62±0.15

*p<0.05, **p<0.01*significant increase than non rebleeding after EVL respectively*.
[a]p<0.05 *significant decrease than non rebleeding after EVL.*

Table-3: Ultrasonographic findings of the studied groups.

	non rebleeding after EVL (n= 71)	rebleeding after EVL (n= 9)
Portal vein diameter	14.04±0.19	13.08±0.74
Portal vein thrombosis	7 (9.86%)	1 (11.1%)
Size of the spleen	15.76±0.21	16.13 ± 0.54
Ascites		
No	22 (31.0%)	1 (11.1%)
Yes	49 (69.0%)	8 (88.9%)**

** *p<0.01 significant increase than non rebleeding after EVL.*

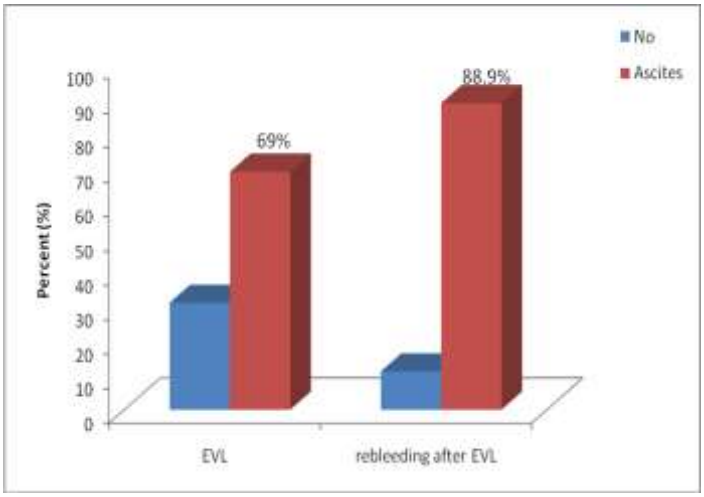

Fig-1: Comparison between two groups regarding ascites.

Table-4: Child-Pugh and MELD scores of the studied groups.

Child-Pugh score	non rebleeding after EVL (n= 71)	rebleeding after EVL (n= 9)
Child A Child B Child C	3 (4.2%) 32 (45.1 %) 36 (50.7%)	0 (0.0%) 1(11.1%) 8(88.9%)*
MELD score	12.35±0.86	20.11±3.26**

* *p*<0.05, ** *p*<0.01 *significant increase than non rebleeding after EVL.*

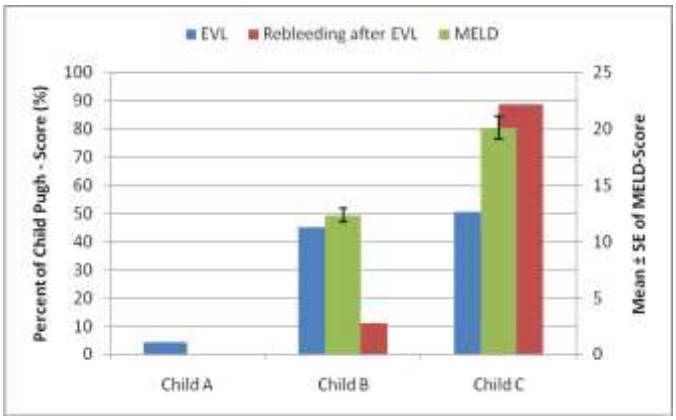

Fig2: Comparison between the two groups regarding MELD score.

Table-5: Comparison between endoscopic findings of the studied groups.

	non rebleeding after EVL (n= 71)	rebleeding after EVL (n= 9)
(1)-Esophageal		
OV GI	1 (1.4%)	0
OV GII	29 (40.8%)	2 (22.2%)
OV GIII	35 (49.3%)	3 (33.2%)
OV GIV	6 (8.5%)	4 (44.4%)**
Extend of OV		
Lower ⅓	28 (39.4%)	2 (22.2%)
Lower ½	23 (32.4%)	0
Lower ⅔	20 (28.2%)	7 (77.8%)**
Number of OV	3.18±0.78	3.77 ± 0.67*
Red sign	67 (94.4%)	9 (100.0)
(2)-Gastric		
Gastric varies	0.45±0.73	0.88±0.6*
Portal hypertensive gastropathy	51 (71.8%)	5 (55.6%)
(4)-Number of rubber bands	4.18±0.13	4.66±0.47
(3)-Number of session of previous intervention	1.45±0.13	2.44±0.37**

*$p<0.05$, **$p<0.01$*significant increase than non rebleeding after EVL respectively*.

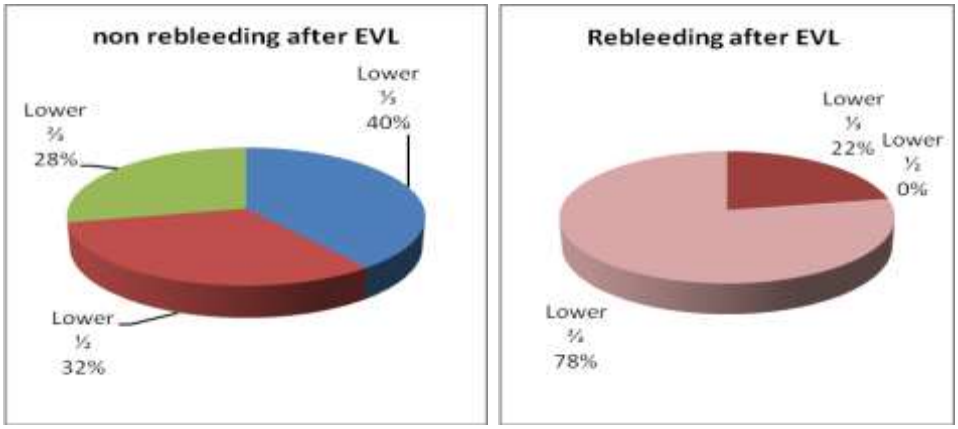

Fig-3: Extend of varices in the esophagus in both groups.

DISCUSSION

Early variceal rebleeding as a vital complication after EVL has not been studied fully. There are only a few studies reporting the possible predictors for early variceal rebleeding after EVL. Despite substantial improvement in overall survival in recent years, the 6-week mortality after variceal bleeding remains discouragingly high; especially in Child-Pugh class C patients, who die either from uncontrolled initial variceal bleeding or early rebleeding, or subsequently from the consequences of infection, liver and renal failure in the first weeks after a bleeding episode [11]. Our results revealed that incidence of early variceal rebleeding following EVL was (11%). Lo GH, [25] reported that the rate of early rebleeding following EVL was between 9% and 19%, which is close to our result. Also it is close to Xu . [13] who reported that incidence of early rebleeding following EVL was (7.6%). On the other hand, Chiang [12] reported rebleeding rate of 23.33%.

Esophageal variceal grade was significantly higher in the early variceal rebleeding after EVL when compared to the non-rebleeding group as large size of varices indicate more venous pressure. This finding was not proved in Xu *et al*. [13] who reported that esophageal varices grade has no significance as in-dependent risk factors for rebleeding after EVL. This can be explained by sampling difference. A significant difference (P< 0.01) was observed in the early variceal rebleeding after EVL group when compared to the non-rebleeding as regard to history of multiple number of sessions of previous intervention. This finding can be explained as the emergency EVL is often supposed to be different from the elective one because of the different patient conditions and technical difficulty. Vanbiervliet G. *et al*; [5] demonstrated that previous variceal bleeding is one of the independent predictive factors for the occurrence of rebleeding after EVL. Florian Petrasch [14] proposed that endoscopist may consider elective EVL as an out-patient procedure. In cases when EVL is performed as an in-patient procedure, one may consider restricting the period of

surveillance after elective EVL to four days. Elective EVL should be done until all varices are eradicated. An excessive application of ligation bands should be avoided. However, we propose to keep patients who have undergone endoscopic band ligation due to acute esophageal haemorrhage under medical surveillance for at least 8-11 days. Regarding the extension of varices our study highlighted that, there was significant difference (p<0.01) between the early variceal rebleeding after EVL group and the non-rebleeding group. This is consistent with Xu *et al.* [13] who reported that Varices that extend along the entire esophagus are much more dangerous than varices that are limited to the middle and lower part. A greater extent of varices often means that more rubber bands are needed, increasing the possibility of rebleeding, however no statically significant difference between the two groups as regard the number of rubber bands was found in this study which can explained by most of cases are almost equal in number of rubber bands applied.

The presence of gastric varies was statistically significant (p<0.05) with a higher prevalence in the early variceal rebleeding after EVL group when compared to the non-rebleeding group. This finding is in agreement with Chiang [12] who reported rebleeding rate of 23.33%. At least 50% were portal hypertensive-related bleeding classified as 14.28% of gastric varices and 42.86% of hypertensive gastropathy sites. On the other hand Gastric varices were not proved to be a predictor factor in Xu *et al*. [13], Vanbiervliet G *et al* [5] and other studies.

Serum albumin was significantly lower in the early variceal rebleeding after EVL group when compared to the non-rebleeding group (p<0.05). This finding was in agreement with LIU Tao WANG *et al* [15] who reported that one of death risk factors of cirrhotic in-patients complicated with esophageal varices bleeding was the presence hypoalbuminemia. Also it agrees with J Grothaus *et al* [16] who reported that lower serum albumin was significantly present in patients with post interventional bleeding. On the other hand Xu . [13] stated that albumin has no significance as independent risk factors for rebleeding after EVL. A higher total bilirubin was statistically highly significant (p<0.01) in the early variceal rebleeding after EVL group when compared to the non-rebleeding group. This finding was in agreement with LIU Tao, WANG [15] who reported that another death risk factor of cirrhotic in-patients complicated with esophageal varices bleeding was the presence elevated total bilirubin level. On the other hand, Xu . [13]. total bilirubin not proved as independent risk factors for rebleeding after EVL.

The presence of ascites was statistically highly significant (p<0.05) in the early variceal rebleeding after EVL when compared to the non-rebleeding group. This finding was in agreement with Xu *et al.* [13] who reported that moderate to excessive volume of ascites was the most dangerous factor predicting post-EVL rebleeding (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 by Moitinho E *et al.* [17], 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.

In our results, patients with end stage liver disease as indicated with Child-Pugh class-C shows significant difference (p<0.05) in the rebleeding group compared to the non rebleeding after EVL. Child-Pugh score was an independent risk factor of post-EVL rebleeding in Xu *et al.* [13]. Yang *et al*.[18] showed that there was a difference in Child-Pugh score between the rebleeding and non-rebleeding groups and 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. Berreta et *al* [19] observed that one of the independent in-hospital mortality predictors was Child-Pugh class C. Statistically significant (p<0.01) higher MELD score was also present in the rebleeding group compared to non rebleeding after EVL. This is similar with the results shown by Chen [20] who demonstrated that the MELD score is an easy and powerful predictor for 6-wk mortality and outcomes of patients with early rebleeding after EVL.

In the present study we found no statistically significant difference between the two groups as regard the INR and prothrombin concentration This finding was in agreement with Vieira da Rocha *et al* [21] who reported that Post-EVL ulcer bleeding was associated with Child C status but not with conventional or expanded coagulation indices in cirrhotic patients without renal failure or infection undergoing elective EVL. These results call into question the common use of prophylactic procoagulants in the elective setting. However Xu *et al.* [13], Li P *et al* [4] stated that PT more than 18 seconds was an independent risk factor of post-EVL rebleeding (OR 11.35, 95% CI: 1.93-66.70).

Finally we found no statically significant difference between the two groups as regard the portal vein thrombosis. This finding was in agreement with Xu *et al.* [13] and can explained by Kayacetin *et al.* [22] who 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. Also Janssen *et al* [23] reported that PVT without liver cirrhosis caused a low variceal bleeding rate, while the rate went up significantly once the cirrhosis presented [24]. These findings suggest that the primary liver disease may be the dominant factor for variceal

bleeding and the prognosis of cirrhosis in patients with PVT depends on the severity of liver disease.

In conclusion the incidence of early variceal rebleeding following EVL was (11%). Poor liver function as indicated by Child-Pugh and MELD scores with endoscopic findings of higher esophageal varices grade, number and extent of esophageal varices, presence of gastric varices and number of session of previous intervention were risk factors contributing for early variceal rebleeding after EVL. A larger number of cases should be studied in controlled randomized study to validate predictors of early variceal rebleeding after EVL.

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