



Incidence and risk factors of early Variceal Bleeding after Esophageal Variceal Ligation

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Abstract

Background and Aim: Liver cirrhosis is a major health problem in Egypt, especially that complicating viral hepatitis [1]. Portal hypertension commonly accompanies the presence of liver cirrhosis. The development of esophageal varices (EV), gastric varices (GV) and portal hypertensive gastropathy (PHG) are the major presentation of portal [2]. Early recurrent bleeding after esophageal variceal ligation (EVL) (rebleeding occurring between 24 h and 14 d after the operation) is fatal [3]. We aimed to assess incidence & risk factors contributing for early variceal bleeding after EVL. **Patients and Methods:** This study was conducted on 80 patients with chronic liver disease who underwent EVL for esophageal varices in the period from the April 2012 till the 30th of June 2013 in Ain Shams university hospital and Theodor Bilharz Research Institute. According to occurrence of early bleeding after EVL, the patients were classified into 2 groups. **Group (1):** None early variceal bleeding. **Group (2):** Early variceal bleeding. **Results:** Our results revealed that the incidence of early bleeding following esophageal variceal ligation was 11% (9 out of 80 patients). Low serum albumin, high BUN and high total bilirubin as laboratory investigations were risk factors contributing for early variceal bleeding after band ligation. Gastric varices, esophageal varices grade and extent of esophageal varices as endoscopic data were risk factors contributing for early variceal bleeding. Also we found that volume of ascites as ultrasonographic finding was a risk factor contributing for early variceal bleeding after EVL. History of previous intervention either by band ligation or injection sclerotherapy and MELD score were risk factors contributing for early variceal bleeding after EVL. **Conclusions:** Incidence of early bleeding in patients with chronic liver diseases who underwent esophageal variceal ligation EVL for esophageal varices was (11%). Patients should be assessed thoroughly according to the risk factors (especially the independent ones) before EVL to minimize rebleeding.

Keywords: Esophageal varices, esophageal variceal ligation Chronic liver disease.

1.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 % [4]. 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 [5].

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 [6].

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 [7]. 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 [7].

2. Patients and Methods:

2.1. Study Design and Duration:

This is a prospective study, during the period from April 2012 till June 2013.

2.2. Patients:

A total of 80 patients with chronic liver disease who underwent EVL for esophageal varices in Ain Shams University Hospital and Theodor Bilaharz Research Institute after signing a written consent.

Inclusion criteria:

All patients with chronic liver disease who underwent EVL for treatment of esophageal varices due to cirrhosis.

Exclusion criteria:

Patients refused to undergo the procedure or to sign the consent.

2.3. Methodology:

2.3.1. Clinical, Laboratory and radiological evaluation:

- i. Full history taking stressing on number of sessions of previous intervention either injection sclerotherapy or band ligation.Laboratory.

- ii. Clinical examination.
- iii. Investigations including: Complete blood picture (CBC), Prothrombin time (PT) and INR, Liver profile (AST, ALT, total bilirubin, direct bilirubin and serum albumin), Renal functions (serum creatinine and blood urea nitrogen).
- iv. Ultrasonography was performed after an overnight fasting stressing on Liver echogenicity, criteria suggestive of chronic liver disease and cirrhosis (loss of homogenous texture to be replaced by speckled coarse texture, irregular liver margins, attenuation of intra hepatic veins, relative enlargement of caudate lobe and atrophy of right lobe (ratio of caudate/right lobe in cirrhosis >0.65) [8], ascites, portal vein diameter and patency and the size of spleen.
- v. Evaluation of the severity of liver cirrhosis was obtained in each cirrhotic patient with Child-Turcotte-Pugh score. This system relies on clinical and laboratory evaluation including ascites, grade of encephalopathy, serum albumin, bilirubin and prothrombin time.
- vi. MELD score was calculated for all patients according the formula score = $[9.57 \times \log \text{creatinine}(\text{mg/dl}) + 3.78 \times \log \text{bilirubin}(\text{mg/dl}) + 11.2 \times \log \text{INR} + 6.4]$ which is done on MELD score web site on internet. [9]

2.3.2. Technique (Upper endoscopy):

Using Pentax EG 2940 scope, the endoscopic procedures followed the guidelines established by the Chinese Endoscopy Institute in 2000 [10]. 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.

A. Esophageal varices grade.

Wehrmann T classified esophageal varices into 4 grades as follows [11]:
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

B. Number of columns of the esophageal varices.

C. Extent of esophageal varices: Middle, lower section or whole.

D. Red sign.

E. Gastric varies.

F. Number of rubber bands applied.

G. Severity of Portal hypertensive gastropathy.

2.3.3 Following EVL:

All patients taken standard doses of proton pump inhibitors (PPIs) for 2 wk. and sucralfate 1 gm. every 8 hours for 1 week. Food intake allowed at the discretion of the physician.

Early bleeding 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 hemoglobin 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.

2.3.4. Statistical Methods:

IBM SPSS statistics (V. 21.0, IBM Corp., USA, 2012) was used for data analysis. Date was expressed as Mean \pm SD for quantitative parametric measures in addition to Median Percentiles for quantitative non-parametric

measures and both number and percentage for categorized data. The following tests were done:

1. Comparison between two independent mean groups for parametric data using Student t test.
2. Comparison between two independent groups for nonparametric data using Wilcoxon Rank Sum test.
3. Chi-square test to study the association between each 2 variables or comparison between 2 independent groups as regards the categorized data.

Power of significance (probability):

- $P > 0.05$ Non-significant.
- $P < 0.05$ Significant
- $P < 0.01$ highly significant.

3.Results

A total of 80 patients with chronic liver diseases were enrolled in this study that underwent EVL for esophageal varices. According to occurrence of early bleeding after EVL, the patients were classified into 2 groups:

- Group (1): none early bleeding including (71) patients.
- Group (2): early bleeding including (9) patients.

From the total number of patients in Group (1), age group was ranging from 28 up to 83 years with mean age 37.15 ± 14.38 . Forty eight (67.6%) patients were males and 23 (32.4%) patients were females. In Group (2), age group was ranging from 50 up to 63 years with mean age 41.8 ± 7.76 . Seven (68.8%) patients were males and 2 (31.3%) patients were females (**Table 1**)

Table (1): Demographic features of the studied groups.

	Group 1 (n= 71)	Group 2 (n= 9)	P value
Age (yrs.) mean \pm SD	37.15 \pm 14.38	41.8 \pm 7.76	0.634
Sex (Female/Male)	23/48 (32.4/67.6%)	2/7 (31.3/68.8%)	0.535

Hematological and biochemical characteristics of the two studied groups showed significant difference between the two groups only as regard serum albumin

(p value = 0.026), BUN (p value = 0.026) and total bilirubin (p value = 0.018) (**Table 2**)

Table (2): Hematological and biochemical characteristics of the studied groups.

	Group 1 (n= 71)	Group 2 (n= 9)	P value
Hemoglobin	9.67±2.18	8.83±1.75	0.63
White blood cells	7.41±5.35	9.46 ± 3.66	0.051
Platelet count	103.08± 70.76	96.77± 70.07	0.802
ALT(U/L)	67.47±36.17	36.33±28.05	0.31
AST(U/L)	41.12±25.69	77.44±78.97	.059
T.BIL (mg/dl)	1.5±0.78	4.34±5.22	0.018
ALB (g/dl)	2.47±0.41	2.07±0.429	0.026
Creatinine(mg/dL)	1.02±0.576	1.56±0.84	0.058
BUN (mg/dl)	25±17.91	44.66±27.79	0.026
PT(second)	16.32±3.95	17.93±4.63	0.341

Regarding ultrasonographic finding, no significant differences were found between the 2 groups regarding portal vein diameter and size of spleen while regarding ascites we found that:

1- In group (1), 22patients (31.0%) had no ascites, 15 patients (21.1%) had mild ascites, 23 patients (32.4%) had moderate ascites and 11 patients (15.5%) had marked ascites.

2- In group (2), only one patient (11.1%) had no ascites, one patient (11.1%) had mild ascites, two patients (22.2%) had moderate ascites and 5 patients (55.6%) had marked ascites. These data showed significant differences between the 2 groups regarding volume of ascites (**figure 1**)

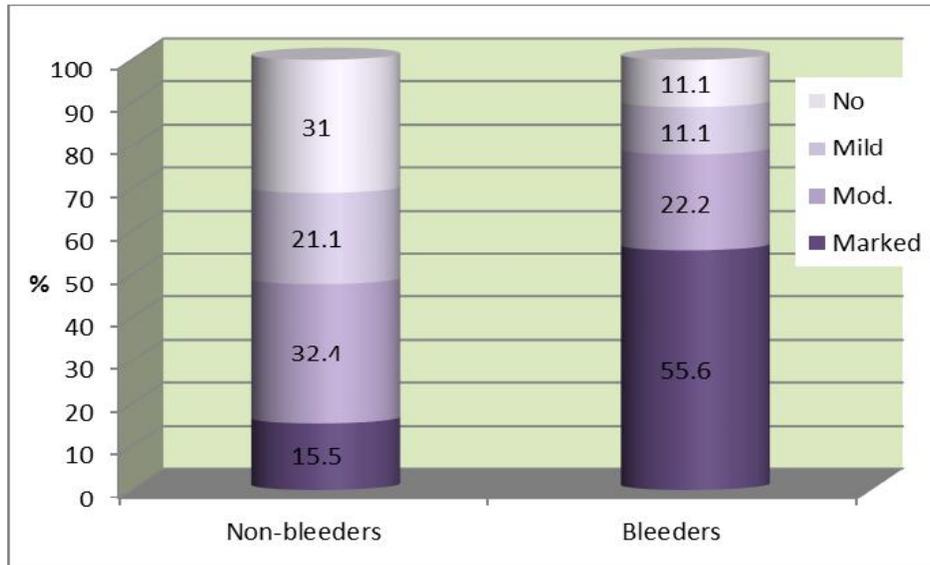


Figure (1): Comparison between two groups regarding ascites.

Our results showed in group (1):3 patients (4.2%) were classified Child A, 32 patients (45.1%) were classified Child B and 36 patients (50.7%) were classified Child C. In Group (2), none of them was classified Child A, only one patient (11.1%) was

classified Child B and 8 patients (88.9%) were classified Child C. Child-Pugh score tend to be a statistically significant (P<0.094) in the early variceal bleeding after (EVL) group when compared to the non-bleeding group (Figure 2)

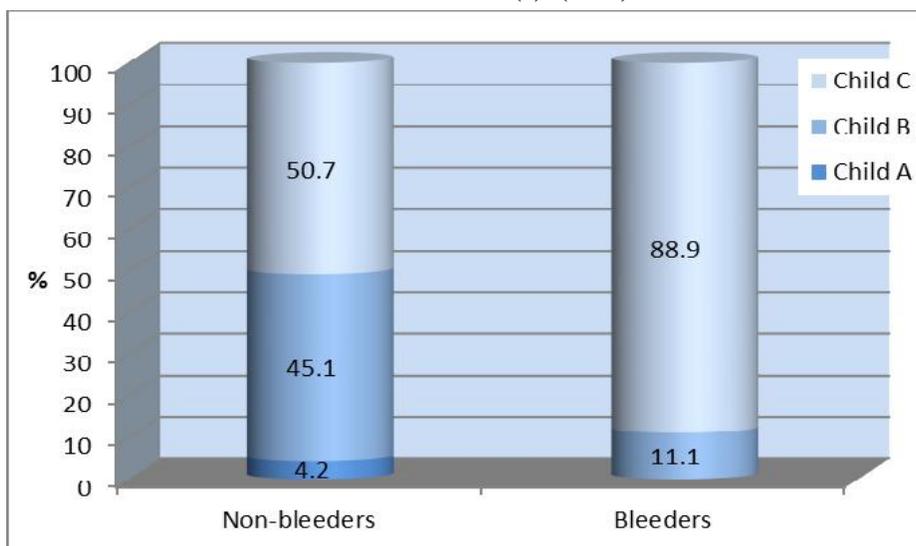


Figure (2) Comparison between two groups regarding Child- Pugh score

Comparing history of number of sessions of previous intervention either by band ligation or injection sclerotherapy between to groups showed that the mean value and standard deviation was (1.45 ± 1.125) for patients with non-early variceal bleeding (group 1) versus (2.44 ± 1.13) for patients with early variceal bleeding (group 2). These data showing highly

significant differences ($P < 0.008$) between the 2 groups regarding number of previous intervention.

Comparison between two groups regarding to red sign, esophageal varices grade, portal hypertensive gastropathy and extent of esophageal varices are shown in **Table (3)**.

Table (3) Comparison between two groups regarding to red sign, esophageal varices grade, portal hypertensive gastropathy and Extent of esophageal varices.

	<i>Group 1 (n= 71)</i>	<i>Group2 (n= 9)</i>	<i>P value</i>
Red sign			
No	4(5.6%)	0(0.0%)	0.465
Yes	67 (94.4%)	9 (100.0 %)	
Esophageal varices grade			
Grade i	1 (1.4%)	0(0.0%)	0.023
Grade ii	29 (40.8%)	0(0.0%)	
Grade iii	35 (49.3%)	2 (22.2%)	
Grade iv	6 (8.5%)	3 (33.3%)	
		4 (44.4%)	
Portal hypertensive gastropathy			
No			0.622
Mild	20 (28.2%)	4 (44.4%)	
Moderate	27 (38.0 %)	3 (33.3%)	
Severe	8 (11.3%)	0 (0.0%)	
	16 (22.5%)	2 (22.2%)	
Extent of esophageal varices			
Lower 1/3	28(39.4%)	2(22.2%)	0.021
Lower 1/2	23(32.4%)	0 (0.0%)	
Lower2/3	20(28.2%)	7 (77.8%)	

1- We can see that red sign was presented in 100% of patients in group (2); while in group (1) was presented in 94.4% of patients.

2- The majority of patients in group (1) were in between grade II and III, while most of patients of group (2) were presented with grade IV varices.

3- Regarding to portal hypertensive gastropathy, in group (1), most of patients had mild portal gastropathy, while most of cases in group (2) had no portalgastropathy.

4- Our data concerning the extent of esophageal varices showed significant difference (P=0.021) in the

early variceal bleeding after (EVL) group when compared to the non-bleeding group.

Our data also showed significant difference between 2 groups as regard presence of gastric varices, while it was not regarding number of esophageal varices or number of rubber bands applied during band ligation (Table 5). Portal vein thrombosis was present in 7 patients among group (1) (9.9 %) with only one patient in group (2) (11.1 %) which is not stastically significant between 2 groups (P<0.904).

Table (5): Comparison between two groups regarding to esophageal varices number, gastric varies, number of rubber bands and portal vein thrombosis.

	<i>Group 1 (n= 71)</i>	<i>Group2 (n= 9)</i>	<i>P value</i>
Esophageal varices number	3.18±0.78	3.77 ± 0.666	0.052
Gastric varies	0.45±0.732	0.888±0.6	0.021
Number of rubber bands	4.183±1.125	4.66±1.41	0.29
Portal vein thrombosis			
No	64 (90.1%)	8 (88.9%)	0.904
Yes	7 (71 %)	1(11.1%)	

Finally there was significant difference between 2 groups when MELD score was studied among each group with the mean value and standard deviation was

(12.35 ± 7.24) for patients with non-early variceal bleeding (group 1) versus (20.11 ± 9.8) for patients with early variceal bleeding (group 2) (Figure 3).

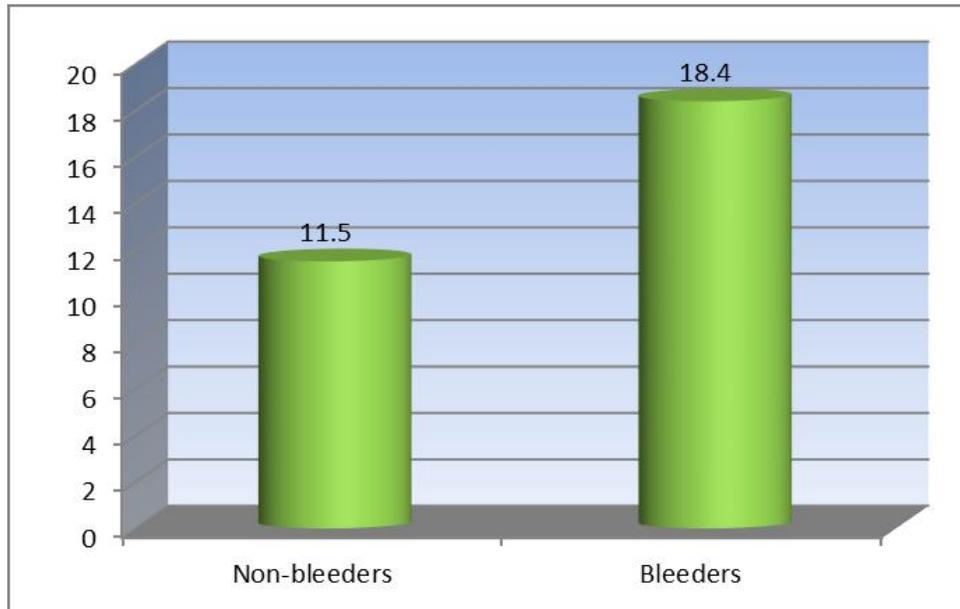


Figure (3) Comparison between two groups regarding MELD score

4. Discussion

Bleeding from esophageal varices accounts for most cirrhosis-related deaths [12]. The annual incidence of new varices in cirrhotic patients is about 5.10% [13] and are present in about 30.40% of compensated patients and in 60% of those who present with ascites [14]. Once diagnosed, the overall incidence of variceal bleeding is in the order of 25% at 2 years in non-selected patients [15]. Mortality from variceal bleeding has decreased substantially from 42% as reported by Graham and Smith [16] to around 20% [17], probably as a result of improved general management (with prophylactic antibiotics) and more effective therapies (endoscopic variceal ligation and new vasoactive drugs) [18]. Despite substantial improvement in overall survival in recent years, the 6-week mortality after variceal bleeding remains discouragingly high; especially in Child-Pugh grade 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 [19].

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. Furthermore, the emergency EVL is often supposed to be different from the elective one because of the different patient conditions and technical difficulty [7]. Following EVL, a local ulcer is commonly found with an ensuing well-described sequence of the pathological changes [20,21]. After strangulation, variceal thrombosis occurs with varying degrees of ischemic necrosis inducing detachment of the rubber band. Then, a shallow ulcer usually occurs that heals within 2–3 weeks, allowing the development of fibrosis in the sub mucosa. In case of premature detachment of the rubber band, before variceal thrombosis, marked alterations of the mucosa can be seen with dilated variceal vessels in necrotic areas. These pathological findings may explain the rare re-bleeding episodes from esophageal ulcers following EVL [21].

Our results revealed that incidence of early bleeding following esophageal variceal ligation was (11%). Lo G and his colleagues [22] reported that the rate of early rebleeding following EVL was between 9% and 19%,

which is close to our result. Also it closed to Xu L and his colleagues [23] who reported that incidence of early rebleeding following EVL was (7.6%).

In the present study, a statistically significant low serum albumin ($P < 0.05$) was present in the early variceal bleeding after (EVL) group when compared to the non-bleeding group. This finding was in agreement with LIU Tao, WANG et al [24] who reported that one of death risk factors of cirrhotic inpatients complicated with esophageal variceal bleeding was the presence hypoalbuminemia. Also it agreed with J Grothaus et al [25] who reported that lower albumin was significantly present in patients with post interventional bleeding. On the other hand Xu L et al [23] stated that albumin has no significance as independent risk factors for rebleeding after EVL.

Higher total bilirubin was statistically significant ($P < 0.05$) in the early variceal bleeding after (EVL) group when compared to the non-variceal bleeding group. This finding was in agreement with LIU Tao, WANG [24] who reported that another death risk factor of cirrhotic inpatients complicated with esophageal variceal bleeding was the presence elevated total bilirubin levels. On the other hand Xu L. et al [23] did not prove total bilirubin as independent risk factors for rebleeding after EVL.

Statically significant volume of ascites ($P < 0.05$) was present in the early variceal bleeding after (EVL) group when compared to the non-bleeding group. This finding was in agreement with Xu L et al. [23] who reported 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 by Moitinho E et al [26], 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.

Our study highlighted that, there was significant difference ($P < 0.05$) between the early variceal bleeding after (EVL) group and the non-bleeding group regard to extension of varices. This is consistent with Xu L et al. [23] 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.

When grading of esophageal varices were studied, a statistically significant ($P < 0.05$) Esophageal varices grade was present in the early variceal bleeding after (EVL) group when compared to the non variceal bleeding group as large size of varices indicate more venous pressure. This finding was not proved in Xu L et al. [23] 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 highly statically significant difference ($P < 0.001$) between the early variceal bleeding after (EVL) group when compared to the non variceal bleeding group as regard history of number of session of previous intervention either band ligation or injection sclerotherapy was observed. This finding can 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 [7] demonstrated that previous upper variceal digestive bleeding one of independent predictive factors for the occurrence of bleeding after EVL. Florian Petrasch [27] proposed that endoscopists may consider elective EBL as an out-patient procedure. In cases when EBL is performed as an in-patient procedure, one may consider restricting the period of surveillance after elective EBL to four days. Elective EBL 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 hemorrhage under medical surveillance for at least 8-11 days.

The results of our study showed that, patients with end stage liver disease as indicated with Child-Pugh score tend to be significant ($P < 0.094$) in the early variceal bleeding after (EVL) group when compared to the non-bleeding group. Child-Pugh score for liver function was an independent risk factor of post-EVL rebleeding in Xu L et al. [23]. Yang MT et al [28] 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 [29] observed that one of independent in hospital mortality predictors was Child Pugh C class ($p = 0.024$).

Gastric varices were present significantly in the early variceal bleeding after (EVL) group when compared to the non-bleeding group. Gastric varices were not proved as risk factor in Xu L et al. , Vanbiervliet G et al [7] and other studies. On the other hand, Chiang et al. [30] reported that the rebleeding rate was 23.33%. At least 50% were portal hypertensive-related bleeding, and classified as 14.28% of gastric varices and 42.86% of hypertensive gastropathy sites.

Surprisingly we did not find statistically significant difference between the two groups as regard the INR and prothrombin concentration This was in agreement with Vieira da Rocha EC et al [31] 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 L et al. [23], Li P et al [3] stated 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 or fibrinolysis acceleration. Therefore, for patients with quite prolonged PT, supplementing vitamin K1 and coagulation factors are necessary before EVL.

A statistically significant MELD score ($P < 0.05$) was present in the early variceal bleeding after (EVL) group when compared to the non-bleeding group. This is similar with the results shown by Chen WC [32] who demonstrated that the MELD score is an easy and powerful predictor for 6 weeks mortality and outcomes of patients with early rebleeding after EVL for EVH.

Finally in our work we found no statically significant difference between the two groups as regard the portal vein thrombosis. Similar results were elicited with

Xu L et al [23] and can explained by Kayacetin E et al [33] 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 HL et al [34] reported that PVT without liver cirrhosis caused a low variceal bleeding rate, while the rate went up significantly once the cirrhosis presented De Franchis R et al [2]. 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.

In conclusion, Incidence of early bleeding in patients with chronic liver diseases who underwent esophageal variceal ligation for esophageal varices was (11%). Patients should be assessed thoroughly according to the risk factors including low serum albumin, BUN, total bilirubin, volume of ascites, presence of gastric varices, grading and extent of esophageal varices,, history of previous intervention and finally MELD score before EVL to minimize rebleeding.

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