ORIGINAL SCIENTIFIC ARTICLE

RISK FACTORS OF ESOPHAGEAL BLEEDING IN CHILDREN WITH VARIOUS ETIOLOGIES OF LIVER CIRRHOSIS – A SINGLE-CENTER REPORT FROM IRAN

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ABBREVIATIONS

AL – Alanine aminotransferase,
APRI – AST to Platelet Ratio Index,
AST – Aspartate aminotransferase,
CHF– Congenital Hepatic Fibrosis,
GSD – Glycogen Storage Disease,
INR – International normalized ratio,
MELD – Model For End-Stage Liver Disease,
PELD – Pediatric End-Stage Liver Disease,
PFIC – Progressive Familial Intrahepatic Cholestasis

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ABSTRACT

Esophageal bleeding is a common complication in patients with liver cirrhosis. In thee present study, our aim was to divulge major factors predicting esophageal bleeding in Iranian children with liver cirrhosis. This was a cross-sectional study including 101 children < 18 years old referred to the Pediatric Endoscopy Unit of Nemazee Teaching Hospital of Shiraz from 2014 until 2016. Children with esophageal varices were included. The patients were divided into two groups including those with and without history of esophageal bleeding. Statistical methods were performed in SPSS 16 software. There were 49 boys and 52 girls. The mean age was 7.74±5.26 years old. A history of esophageal bleeding was observed in 53 (52.4%). In univariate analyses, significant relationships were found between esophageal bleeding and varices size (P=0.001), Child-Pugh score (P=0.01), age of bleeding initiation (P<0.001), serum creatinine (P=0.01), and serum sodium (P=0.002). There was no statistically significant difference in the mean of PELD/MELD score among children with (12.34±12) and without (14.61±17.51) history of esophageal bleeding (P=0.5). Among various etiologies of cirrhosis, a significant association was observed between autoimmune hepatitis and the history of esophageal bleeding (P=0.01). Regarding the clinical importance of esophageal bleedings in children with liver cirrhosis, it is recommended to further divulge the risk factors predisposing to this event.

Keywords: *esophageal varices, liver cirrhosis, prognosis, risk factors, esophageal bleedin.*

INTRODUCTION

Liver cirrhosis is a late stage of chronic hepatic disorder. Cirrhosis is characterized with liver fibrosis and thedevelopment of a dysregulated nodular structure (1). Advanced liver fibrosis is seen in many liver diseases and it results from the accumulation of extracellular matrix components (e.g. collagen, glycoproteins, and proteoglycans) within hepatocytes (2). Cirrhosis can be associated with a wide range of complications including ascites, encephalopathy and esophageal bleeding (3, 4).

Esophageal bleeding is one of the main complications associated with high mortality and morbidity rates in children with cirrhosis (5, 6). This sequela is the outcome of portal hypertension and esophageal varices (7). The overall incidence of esophageal varices has been described in 6% of cirrhotic patients (8). Bleeding from esophageal varices has been noted in 5-19% of children (5, 6, 9). In patients with esophageal varices, the annual risk of esophageal bleeding has been reported in 4% increasing to 15% of patients with large varices (7). Also, the risk of bleeding has been reported in 10-75% of untreated patients (10). The 35-day mortality risk following gastrointestinal bleeding has been reported in 35% of children with esophageal varices (5).

Esophageal bleeding in children is treated according to the protocols available for adults including pharmaceutical, endoscopy and surgical interventions (11). Although beta-blockers and endoscopic band ligation have been noted as prophylactic managements for esophageal bleeding (6, 12), these methods have not always been effective and may even worsen the condition in some cases (13). Endoscopic band ligation has been suggested as a prophylactic intervention in children at high risk of esophageal bleeding (9). There is an incomplete understanding of risk factors predisposing to esophageal bleeding in children with liver cirrhosis. In this study, we described the risk factors, clinical and laboratory features, as well as endoscopic findings in cirrhotic children with esophageal bleeding.

PATIENTS AND METHODS

This was a cross-sectional study which included children <18 years old with liver cirrhosis referred to the Pediatric Endoscopy Unit of Nemazee Teaching Hospital affiliated with Shiraz University of Medical Sciences from 2014 until 2016. The children were evaluated for possible esophageal varices and those without esophageal varices in endoscopy examination were excluded from the study. Finally, 101 children with liver cirrhosis and esophageal varices were analyzed.

The patients were divided into two groups - those with and without history of esophageal bleeding.

Demographic data including age, sex, duration and etiology of liver cirrhosis, age of the first bleeding episode, history of encephalopathy and ascites and other paraclinical information (albumin, bilirubin, liver enzymes, creatinine, platelet, and sodium) were recorded. The PELD/MELD and Child-Pugh score were also determined.

Esophageal varices were categorized based on their sizes to small, medium, and large groups according to the classification described previously (14). In patients with multiple-size varices, the size of the largest one was considered. Furthermore, the presence of vessels on vessel, red spots, gastric varices and hypertensive gastropathy were sought in endoscopy.

Statistical methods were performed in SPSS 16 software. Nominal variables were described by frequencies and their relationships with each other were checked by Chi-square test. The distribution of quantitative variables was checked by Kolmogorov-Smirnov test. Mann-Whitney U test and independent sample student t-test were used as non-parametric and parametric tests for comparing mean values of quantitative variables between the study groups.

RESULTS

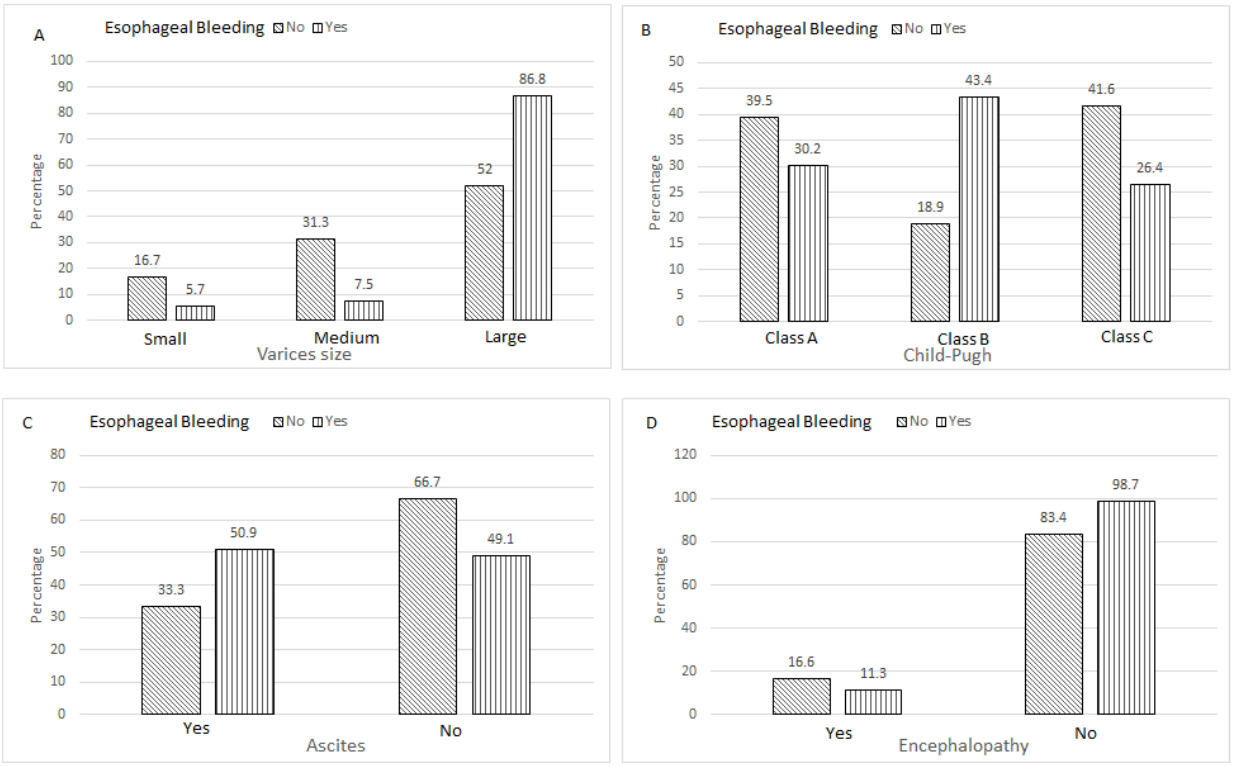
101 children <18 years old including 49 boys and 52 girls with liver cirrhosis and esophageal varices were included in this study. The mean age was 7.74±5.26 years old. Propranolol was administrated as prophylaxis for all patients. The band ligation was additionally used as prophylaxis for patients with medium and large size varices. Secondary therapy included sclerotherapy for children < 3 years old and ligation band for those >3 years old.

From 101 patients, 53 (52.4%) showed history of esophageal bleeding. Significant relationships were found between varices size (P=0.001) and Child-Pugh score (P=0.01) and esophageal bleeding (Figure 1).

There was no statistically significant difference in the mean PELD/MELD scores among children with (12.34±12) and without (14.61±17.51) history of esophageal bleeding (P=0.61). There were also significant differences between the two groups regarding the age of bleeding initiation (P<0.001), serum creatinine (P=0.01) and sodium (P=0.002) levels (Table 1).

No evidence of red spots or vessel on vessels was observed in endoscopy findings. However, two patients showed hypertensive gastropathy in endoscopy evaluation. Among various etiologies of cirrhosis, a significant association was observed between autoimmune hepatitis and the history of esophageal bleeding (P=0.01) (Table 2).

Figure1. Association of esophageal bleeding with main clinical parameters in 101 cirrhotic children (53 with and 48 without esophageal bleeding)



Significant differences were found in the distributions of varices size (P=0.001, A) and Child-Pugh classes (P=0.01, B) between children with and without esophageal bleeding. There were no significant differences in the distribution of either ascites (C) or encephalopathy (D) in children with or without esophageal bleedings.

Table 1. Association of esophageal bleeding with main laboratory parameters in 101 cirrhotic children

Laboratory parameters	**Esophageal bleeding**		**P**
	Yes N=53 n (%)	No N=48 n (%)	
MELD/PELD Score	12.34±12	14.61±17.51	0.5
Age (years)	7.5±5.14	7.46±5.26	0.97
Duration of hospitalization (days)	4.04±3.35	3.24±2.90	021
Bleeding age (years)	5.58±4.75	-	NA
Albumin (mg/dl)	4.25±4.75	3.7±0.74	0.53
Total Bilirubin (mg/dl)	5.97±7.58	7.55±10.92	0.47
INR	1.07±1.03	2.46±2.43	0.47
AST (IU/l)	157.54±316.81	164.72±193.78	0.33
ALT (IU/l)	107.34±202.62	118.81±187.48	0.70
Platelet (10^3/ul)	117.57±87.29	117±76.78	0.73
Creatinine (g/dl)	0.54±0.31	0.35±0.22	0.01
Na (mEq/l)	138.65±4.23	136±3.55	0.002
APRI	6.65±10.34	6.05±7.61	0.55

PELD; Pediatric End-Stage Liver Disease, MELD; Model For End-Stage Liver Disease, INR; International normalized ratio, APRI: AST to Platelet Ratio Index, AST; Aspartate aminotransferase, ALT; Alanine aminotransferase

Table 2. Association of esophageal bleeding with underlying diseases in 101 cirrhotic children

Underlying disease	Esophageal bleeding		P
	Yes N=53 n (%)	No N=48 n (%)	
Biliary atresia	12 (22.9)	14 (29.3)	**0.969**
Autoimmune hepatitis	7 (13.2)	2 (4.1)	**0.01**
Willson disease	1 (1.8)	2 (4.1)	**0.57**
PFIC	1 (1.8)	1 (2)	**1.00**
Neonatal hepatitis	1 (1.8)	2 (4.1)	**0.57**
CHF	4 (7.6)	2 (4.1)	**0.12**
Cryptogenic	3 (5.7)	1 (2)	**0.62**
Portal vein thrombosis	6 (11.4)	5 (10.7)	**0.13**
HPV	0 (0)	1 (2)	**0.43**
Galactosemia	1 (1.8)	0 (0)	**1.00**
Caroli disease	1 (1.8)	0 (0)	**1.00**
Gauncher disease	2 (3.7)	1 (2)	**0.50**
GSD	1 (1.8)	1 (2)	**1.00**
Unkwon	12 (22.9)	16 (33.6)	**0.58**
Lipodystrophy	1 (1.8)	0 (0)	**1.00**

PFIC; Progressive Familial Intrahepatic Cholestasis, CHF; Congenital Hepatic Fibrosis, GSD; Glycogen Storage Disease

DISCUSSION

Bleeding from esophageal varices is one of the important causes of morbidity and mortality in cirrhotic children. Therefore, it is critical to timely detect esophageal bleeding, divulge its risk factors, and appropriately manage its complications. Overall, 53 (52.4%) out of 101 evaluated cirrhotic children represented history of esophageal bleeding in our study. According to our findings, no significant relationships were found between the history of bleeding and encephalopathy, gastric varices, hypertensive gastropathy, and PELD/MELD scores. On the other hand, esophageal bleeding was significantly associated with Child-Pugh score, varices sizes, the age of bleeding initiation, serum sodium and creatinine levels and autoimmune hepatitis. Nonetheless, neither of these parameters remained an independent significant risk factor for esophageal bleeding in multivariant analyses.

Esophageal bleeding should be considered an alarming phenomenon to think of liver transplantation in cirrhotic patients (15). In fact, esophageal bleeding has been noted as an independent predictor of survival in patients with liver cirrhosis (16). In a recent report on children with chronic liver diseases of various etiologies, thrombocytopenia, hypoalbuminemia and splenomegaly were identified as risk factors of esophageal bleeding (17). In our study, however, platelet count and serum albumin were not significantly different comparing children with or without history of esophageal bleeding. Nevertheless, similar to our report, there were no associations between the risk of esophageal bleeding and serum bilirubin, liver enzymes and INR in the recent report (17). As well, no significant deviation was noted in the distribution of liver diseases etiologies in the recent report (17). Instead, we here found that autoimmune hepatitis may be a potential risk factor for esophageal bleeding in cirrhotic children. Further studies should yet be done to ascertain a definite association between autoimmune hepatitis and esophageal bleeding. Other significant risk factors for esophageal bleeding in cirrhotic patients have been noted as defects in the hemostatic pathway (18), viral load in viral-infection associated cirrhosis (19), the size of esophageal varices (20-23), Child-Pugh score (23), serum fibrinogen level (20), presence of gastric varices and hypertensive gastropathy (7, 9, 20-24), as well as the presence of red spots (20, 21, 23-26). In addition to these, we here noticed that serum sodium and creatinine levels may have a role as predictors of esophageal bleeding in cirrhotic children. Hypertensive gastropathy was noted in two of our patients, while no red spots were found in endoscopic evaluations. As mentioned, varices size and Child-Pugh score were associated with the risk of esophageal bleeding in our study as well. Although these were significant factors in univariate analysis, the results were not significant in multinomial regression analysis which may root in the relatively low power of the study. Splenomegaly and hypertension have also been noted as independent risk factors for esophageal bleeding. In present study; however, we did not assess these two factors in our patients. For appropriate and timely management of esophageal bleeding it is inevitable to develop risk stratifying parameters and reliable predicting factors. Liver stiffness has been a promising indicator of

esophageal varices and esophageal bleeding delivering sensitivity, specificity, positive predictive value, and negative predictive value of respectively 83%, 62%, 76.2% and 71.3% with the area under curve value of 0.780 at 31 kPa cut off for predicting significant esophageal bleeding (27).

The study limitations included not reporting splenomegaly and hypertension in the patients. In conclusion, regarding the clinical importance of esophageal bleeding in children with cirrhosis, it is recommended to divulge more details on the risk factors predisposing to this complication in future studies. Also, developing an updated universal guideline on the risk factors, diagnosis, classification, prognosis and treatment of esophageal varices in children is warranted.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national) and the Helsinki Declaration of 1975, as revised in 2013. Voluntary written and informed consent was obtained from each participant prior to enrollment in the study

COMPETING INTERESTS

There are no conflicts of interest.

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