Original Article

Laboratory Predictors of Esophageal Varices in Children with Chronic Liver Disease

GU Ahmed[1], MM Hossain[2], SK Halder[3], S Sultana[4], MN Hossain[5], KA Syfullah[6], ASMB Karim[7], AFM Pervez[8], MK Hassan[9]

Abstract:

Variceal bleeding results as a consequence of portal hypertension and it is a leading cause of morbidity and mortality of children with chronic liver disease (CLD). Upper gastrointestinal endoscopy is the only confirmatory tool for detecting esophageal varices but due to its invasive nature, high cost and lack of available facilities for pediatric endoscopy, alternative laboratory predictors are essential. In this study, we aimed at identifying laboratory predictors that may predict the presence of esophageal varices in children with CLD. This cross-sectional study was done at the department of Pediatric Gastroenterology and Nutrition, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, from July 2008 to June 2010. Fifty consecutive children with CLD, aged 3-15 years of both sexes, who had no history of active/recent variceal bleeding, taking beta blockers or surgery for esophageal varices were included in the study. All patients underwent history and physical examination. Venous blood of the patients was taken for laboratory analysis of serum bilirubin, serum alanine aminotransferase, serum albumin, platelet count and International Normalization Ratio (INR). Later, upper gastrointestinal endoscopy of the patients were done. Based on endoscopic findings children were divided into two groups. Group-I: CLD with esophageal varices included 29 children and Group-II: CLD without esophageal varices included 21 children. A univariate analysis was initially done on laboratory variables followed by a logistic regression analysis to identify the independent variables associated with presence of esophageal varices. Then performance of these independent variables were analyzed using upper gastrointestinal endoscopy as the gold standard test. Out of 50 patients 30 were male. Male-female ratio was 1.5:1. Fifty eight percent (29 out of 50) had esophageal varices. Amongst all the laboratory variables, thrombocytopenia (platelet count <150000/mm^3) was an independent predictor of esophageal varices (p=0.018). Thrombocytopenia showed good sensitivity and specificity (82.7% and 80.9% respectively) to be used as a screening test for predicting esophageal varices in children with chronic liver disease. Thrombocytopenia can be used as an independent predictor for esophageal varices in children with chronic liver disease.

Key words: Chronic liver disease, Esophageal varix, Thrombocytopenia, Children.

Introduction:

Chronic liver disease is a significant cause of morbidity and mortality both among the children and adults[1].

1. Dr. Gias Uddin Ahmed, MBBS, FCPS (Pediatrics), MD (Pediatrics), Assistant Professor (Pediatrics), Faridpur Medical College, Faridpur.

2. Dr. Md. Monir Hossain, MBBS, MD (Pediatrics), Assistant Professor (Pediatrics), Faridpur Medical College, Faridpur.

3. Dr. Swapan Kumar Halder, MBBS, MCPS (Pediatrics), MD (Pediatrics), Assistant Professor (Pediatrics), Sher-E-Bangla Medical College, Barishal.

4. Dr. Sabnam Sultana, MBBS, FCPS (Obstetrics and Gynaecology), Junior Consultant (Gyne and Obs), Faridpur Medical College Hospital, Faridpur.

5. Dr. Mohammad Neamat Hossain, MBBS, MD (Neonatology), Assistant Professor (Neonatology), Faridpur Medical College, Faridpur.

6. Dr. Khalid Ahmed Syfullah, MBBS, MD (Pediatrics), Assistant Professor (Pediatrics), Faridpur Medical College, Faridpur.

7. Prof. ASM Bazlul Karim, MBBS, FCPS (Pediatrics), Professor and Chairman, Department of Pediatric Gastroenterology and Nutrition, Bangabandhu Sheikh Mujib Medical University, Dhaka.

8. Dr. Abu Faisal Md. Parvez, MBBS, MD (Neonatology), Assistant Professor (Neonatology), Faridpur Medical College, Faridpur.

9. Dr. Md. Kamrul Hasan, MBBS, DCH, Senior Consltant, Faridpur Medical College Hospital, Faridpur.

Address of correspondence :
Dr. Gias Uddin Ahmed, MBBS, FCPS (Pediatrics), MD (Pediatrics), Assistant Professor (Pediatrics), Faridpur Medical College, Faridpur.
Mobile: +88-01711979470, E-mail: gias2003@gmail.com

Several serious complications, such as the development of esophageal varices and gastrointestinal bleeding are related to the advanced stage of chronic liver disease[2,3]. Worldwide, a large number of people suffer and die because of these complications. Moreover, during the early stages, people tend to ignore the symptoms or sometimes take local or herbal medications. In most of the cases, by the time they are diagnosed with CLD, almost half of them had developed compensated disease with esophageal varices and more than half of them had decompensated disease with ascites[4]. The rate of developing esophageal varices increases rapidly with time. Incidence of esophageal varices increases to 28% at the end of the third year of the disease[5].

Among the many complications of CLD, bleeding from the ruptured esophageal varices takes nearly 30-50% lives of the adults within the first week of the bleeding[6]. For the children however, the mortality rate ranges from 5-19% which is lower than the adults but still noticeable[2,7-11]. Mortality rate increases in case of rebleeding and without endoscopic intervention, the risk of rebleeding is almost in 60% cases[12].

Additionally, the risk of bleeding increases with time, annually 10-12% small varices progress to large varices and based on the size of the varices, the risk of bleeding also increases from 5% to as high as 15%[13-15].

To reduce the incidence of morbidity and mortality related to complications of CLD, early detection of patients at risk of variceal bleeding is essential. Till now, upper gastrointestinal endoscopy has been the best method for diagnosing the presence of esophageal varices. However, in case of children, such invasive procedure requires additional expertise[16]. Moreover, facilities for endoscopy is not available at all centers.

For the last few years, the emphasis has been given for the laboratory parameters for prediction of esophageal varices. Nevertheless, these studies are mostly centered on searching the parameters for the adults. Very few attempts have been taken for identifying the predicting parameters for the children. In clinical practice, recommendations for the adults are still used for the management of pediatric patients, which might not be adequate due to the age difference[17]. At the same time, upper gastrointestinal endoscopy which might be needed to perform several times during the lifetime of a child is very troublesome.

So, it is urgent to understand the laboratory predictors of esophageal varices for the pediatric group of populations. This study was undertaken to find out the laboratory variables that might independently predicts the presence of esophageal varices in children with chronic liver disease. Understanding the predictors can help to estimate the burden, identify the children at risk and initiate early prophylaxis measures to reduce the morbidity and mortality related to the esophageal varices in children with chronic liver disease.

Materials and Method:

This cross-sectional study was conducted from July 2008 to June 2010 at the Department of Pediatric Gastroenterology and Nutrition, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. All the admitted children, aged 3-15 years of both sexes, diagnosed with chronic liver disease were selected as the study population. Active or, recent (within two weeks) upper gastrointestinal bleeding, patients on β blocker therapy, patients with history of endoscopic sclerotherapy or band ligation, history of previous surgery for portal hypertension, and patients unsuitable for endoscopy were excluded. A total of 50 patients who fulfilled the enrollment criteria were included in the study. Before the enrollment, written informed consent from either of the parents was taken.

At the time of entry, a detailed history of the patients was recorded in a structured questionnaire. Then, 6 ml of venous blood was drawn aseptically and taken into three containers for laboratory workup. Serum bilirubin, serum alanine aminotransferase and serum albumin were done at the Department of Biochemistry, BSMMU by an autoanalyzer (Synchron CX 9 ALX, clinical system by Beckman Coulter, USA). Platelet count was done at the Department of Clinical Pathology, BSMMU by an autoanalyzer (Sysmex, XT-2000i, Japan) and then checked manually by a single pathologist. International Normalization Ratio (INR) was done at the Department of Hematology, BSMMU by an autoanalyzer (Sysmex CA-500, Japan). Results of the investigations were collected and recorded in the structured data collection form.

Later, all CLD patients underwent upper gastrointestinal endoscopy to see the presence or absence of the esophageal varices. A single gastroenterologist did all the endoscopy at Gastroenterology department by video endoscope (GIF Q 150, Olympus, Japan). Based on the upper gastrointestinal endoscopy findings, the CLD patients were divided into two groups. Twenty nine patients with esophageal varices were assigned in Group I and 21 patients without esophageal varices were assigned in Group II. When esophageal varices were present, they were classified into three grades according to Japanese Research Society for portal hypertension[18]; Grade I (small caliber): small non tortuous varices, Grade II (medium caliber): slightly wide and tortuous varices occupying less than one third of the esophageal lumen, Grade III (large caliber): nodular varices, similar to rosary beads, occupying more than one third of the esophageal lumen.

After data collection, they were checked manually and were analyzed by SPSS (Statistical Package for Social Science) Version 12 (SPSS Inc., Chicago, IL USA). We performed Student's t-test for continuous variables and Chi-square test (χ^2) for categorical variables to see the association of various laboratory variables with the presence of esophageal varices. Alpha level was set at 0.05. Initially, univariate analysis followed by multiple logistic regression analysis of laboratory variables were done to identify independent predictors for the presence of esophageal varices. Later, the performance of each significant variables was evaluated.

Ethical permission for this study was taken from the Ethical Review Committee (ERC) of Bangabandhu Sheikh Mujib Medical University.

Results:

Among the 50 patients with CLD in the study, 29 patients with esophageal varices were assigned in group I and 21 patients without esophageal varices were assigned in group II. In both groups,

most of the patients were in the 5-10 years age group but the age difference was not statistically significant ($p = 0.615$). Mean age was 10 years in group I and 9.5 years in group II (Table I).

Table I: Distribution of patients according to blood group.

Age in years	Group I n = 29 (%)	Group II n = 21 (%)	p value
<5	1 (3.4)	2 (9.5)	
5-10	16 (55)	11 (52.4)	0.615
>10	12 (41.2)	8 (38.1)	
Mean ± SD (years)	10.0 ± 3.0	9.5 ± 3.1	
Range (years)	3-15	3-14	

Male-Female ratio to the study patients were 1.5:1(60% male vs 40% female). Percentage of male participants were higher than female in both groups. However, the difference was not statistically significant (p.0.725) (Table II)

Table II: Sex distribution of studied patients

Sex	Group I n = 29 (%)	Group II n = 21 (%)	Total n = 50 (%)	p value
Male	18 (62.1)	12 (57.1)	30 (60)	0.725
Female	11 (37.9)	9 (42.9)	20 (40)	

Wilson's disease was the predominant cause of chronic liver disease in both groups. It comprises 37.9 % (11 out of 29) cases in group I and 47.6 % (10 out of 21) in group II. Hepatitis B virus was the etiology in 17.2% (5 out of 29) cases in group I and 19 % (4 out of 21) in group II. Etiology were unknown in more than one third of cases in both groups. Autoimmune hepatitis was 3.4% (1 out of 29) and biliary cirrhosis from cholestatic hepatitis was 3.4% (1 out of 29) cases in group I and none in group II (Table III).

Table III: Etiology of chronic liver diseases

Etiology	Group I n	Group I %	Group II n	Group II %	Total n	Total %
Wilson's disease	11	37.9	10	47.6	21	42.0
Hepatitis B virus	5	17.2	4	19.0	9	18.0
Autoimmune hepatitis	1	3.4	0	0.0	1	2.0
Biliary cirrhosis from cholestatic hepatitis	1	3.4	0	0.0	1	2.0
Cause unknown	11	37.9	7	33.3	18	36.0

Among the 50 patients, 29 had varices found on endoscopic examination (Group I). Among them, 34.5% had small caliber, 31.0% had medium caliber, and 34.5% had large caliber varices (Table IV).

Table IV: Grading of esophageal varices from endoscopic findings of studied patients

Esophageal varices	Group I n = 29 (%)	Group II n = 21 (%)
Small caliber	10 (34.5)	0 (0.0)
Medium caliber	9 (31.0)	0 (0.0)
Large caliber	10 (34.5)	0 (0.0)

Serum bilirubin, serum alanine aminotransferase (ALT), serum albumin and INR were evaluated in all patients and we found no significant difference among patients having esophageal varices and those without varices. However, we observed that platelet count <150000/mm^3 was statistically significant ($p = 0.018$) between the two groups (Table V).

Table V: Laboratory variables of studied patients

Laboratory variables	Group I n = 29 (%)	Group II n = 21 (%)	p value
Serum bilirubin (mg/dl)			
<1.2	5 (17.2)	3 (14.3)	0.549
≥1.2	24 (82.8)	18 (85.7)	
ALT (U/L)			
<60	7 (24.1)	3 (14.3)	0.312
≥60	22 (75.9)	18 (85.7)	
Serum albumin (g/dl)			
<3.5	24 (82.8)	18 (85.7)	0.549
≥3.5	5 (17.2)	3 (14.3)	
Platelet count /mm^3			
<150000	15 (51.7)	4 (19.0)	0.018
≥150000	14 (48.2)	17 (81.0)	
INR			
<1.3	3 (10.3)	6 (28.6)	0.100
≥1.3	26 (89.7)	15 (71.4)	

To see whether platelet count (<150000/mm^3) can independently predict the presence of esophageal varices, multiple logistic regression analysis were done. Furthermore, the result showed that thrombocytopenia (platelet count <150000/mm^3) could independently predict the presence of esophageal varices (Table VI).

Table VI: Multiple logistic regression analysis of the laboratory variables.

Variable	Coefficient	Odds ratio (OR)	95% CI	*p* value
Serum bilirubin 1.2 mg/dl	0.070	0.80	0.13-4.63	0.951
serum alanine aminotransferase 60 U/L	0.344	0.37	0.07-1.86	0.707
Serum albumin < 3.5 g/dl	0.237	0.74	0.15-3.51	0.668
Platelet count (<150000/mm^3)	0.943	4.55	1.06-21.06	0.018
INR 1.3	0.991	0.61	0.63-0.98	0.259

Performance of thrombocytopenia (platelet count <150000/mm^3) was evaluated for prediction of esophageal varices (Table VII) and results showed the sensitivity of 82.7%, specificity of 80.9%, accuracy of 84.0%, PPV of 78.9%, NPV of 54.8%, LR+ of 2.7 and LR- of 0.6 (Table VII).

Table VII: Performance of thrombocytopenia for prediction of esophageal varices

Platelet count	Endoscopy		Total
	Varix present	Varix absent	
Thrombocytopenia present (Platelet count <150000/mm^3)	24	4	28
Thrombocytopenia absent (Platelet count >150000/mm^3)	5	17	22
Total	29	21	50

* Sensitivity   82.7%
* Specificity   80.9%
* Accuracy   84.0%
* Positive predictive value (PPV)   78.9%
* Negative predictive value (NPV) 54.8%
* Positive likelihood ratio (LR+)   2.7
* Negative likelihood ratio (LR-)   0.6

Discussion:

Variceal bleeding is one of the severe complications of CLD. Increasing prevalence of CLD is associated with an increased incidence of variceal bleeding, and ultimately it results in significant morbidity, mortality and health care cost. Studies have found that the beta-blockers can be used as primary prevention of variceal bleeding in patients with a high risk of varices. On the other side, endoscopy for early detection of varices is both invasive and challenging to find in most of the centers. Non-invasive procedures such as laboratory parameters are thus essential for identifying the risk groups and to take early preventive measures. So that we can ultimately reduce the morbidity and mortality associated with variceal bleeding of the children with CLD. However, limited studies regarding the laboratory predictors, especially for pediatric patients is a drawback for planning effective preventive measures. In our current study, we aimed at finding laboratory predictors for identifying the CLD patients who are at risk of development of varices.

In our study, 58% of the patients had esophageal varices which correspond to the findings of Fagundes et al where they reported that the prevalence of esophageal varices among cirrhotic children were 52%[17].

We also found male predominance among the patients (the male-female ratio was 1.5:1). However, the difference was not statistically significant (*p* = 0.725). Similar findings were observed by Schepis et al, Gill et al and Sarangapani et al[18-21]. We also have not found any association of the age of the patients with the development of varices. It is also consistent with the findings of Thomopoulos et al[22].

Thrombocytopenia in patients with cirrhosis has historically been attributed to hypersplenism due to portal hypertension[6]. However recent studies have suggested that thrombocytopenia in some cirrhotics can occur independently of portal hypertension and is mediated through an inadequate synthesis of thrombopoietin or rapid degradation[6,21].

We observed that, among the laboratory variables, thrombocytopenia (platelet count <150000/mm^3) independently predicted the presence of esophageal varices (OR, 4.55; 95% CI, 1.06-21.06; p value 0.018 with a sensitivity of 82.7% and specificity of 80.9%).

Thrombocytopenia has been seen in different studies as a strong predictor for the presence of esophageal varices. Platelet count was repeatedly found in different studies to be a predictive marker of esophageal varices[23-25].

It was also observed from the present study that serum bilirubin, ALT, serum albumin and INR have no significant association (*p* value 0.778, 0.390, 0.778 and 0.097 respectively) in patients with or without esophageal varices. These results match mostly with the results of the study done by Sharma and Aggarwal[4].

In the present study, it was found that thrombocytopenia (platelet count <150000/mm^3) is an independent predictor of esophageal varices. Thrombocytopenia also showed an excellent sensitivity of 82.7%. Predictors of esophageal varices must have a high sensitivity, even at the cost of a lower specificity, to ensure that the patients with varices are not missed[26]. Our findings correlate with the study by Ghana et al[16].

So, it can be said that thrombocytopenia is a vital laboratory predictor for esophageal varices in children with chronic liver disease. Thrombocytopenia can independently be used to predict esophageal varices in children with chronic liver disease.

Conclusion:

To prevent significant consequences of variceal bleeding of the children with CLD, non-invasive, cost-effective laboratory predictor is urgent. Based on the finding of our study, we can conclude that thrombocytopenia can be used as an independent predictor for esophageal varices in children with CLD.

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