Assessment of Chronic Liver Disease (CLD) Based on Esophageal Varices in Children

ABSTRACT

Background: Chronic Liver Disease (CLD) is a complex and often debilitating condition that affects individuals of all ages, including children. Within pediatric CLD, one critical aspect that demands careful evaluation is the presence and severity of esophageal varices. If left untreated, these enlarged, fragile blood vessels in the esophagus can lead to life-threatening bleeding. The assessment of esophageal varices plays a pivotal role in managing and prognosis of children with CLD.

Aim of the study: The study aims to measure laboratory parameters and calculate serum liver fibrosis scores in CLD children.

Methods: This retrospective study analyzed 24 pediatric patients diagnosed with esophageal varices in Chronic Liver Disease (CLD) at the Department of Pediatric Gastroenterology & Nutrition, BSMMU, Dhaka, Bangladesh, over two years from April 2019 to October 2021. Ethical standards were adhered to with informed consent and ethical committee approval.

Result: According to the diagnoses, 50% of the patients were identified as having Wilson's disease. Notably, 16.7% of the patients presented with Grade 4 esophageal varices. In terms of laboratory parameters, the median hemoglobin level was 10.2 gm/dl, the total leukocyte count was 6300/mm3, the platelet count had a median of 90000/µL, the bilirubin level had a median of 2.7 gm/dl, ALT had a median of 57 U/L, AST had a median of 134.5 U/L, GGT had a median of 132 U/L, INR had a median of 1.6, albumin had a median of 25 gm/dl, and cholesterol had a median of 105 mg/dl. Lastly, the median liver stiffness was recorded as 13.1 kPa, with an interquartile range (IQR) spanning from 10.3 to 21.

Conclusion: This study highlights the importance of early detection and management of esophageal varices in children with CLD, as they are crucial prognostic indicators for underlying liver conditions. By integrating these clinical tools and parameters, healthcare providers can make informed decisions regarding the management and treatment of children with CLD. Early identification of esophageal varices and a comprehensive assessment of the liver's functional status are essential in improving the overall care and outcomes for pediatric patients with chronic liver disease, ensuring timely intervention and support to enhance their quality of life.

Keywords: Assessment, Chronic Liver Disease (CLD), Esophageal Varices

INTRODUCTION

Chronic Liver Disease (CLD) is a formidable adversary in pediatric healthcare, signifying a relentless, irreversible alteration in hepatic structure that often culminates in the direst of complications, including cirrhosis a condition that can herald premature mortality. Within the pediatric age group, the primary instigators of CLD are Wilson's disease (22%), hepatitis, and autoimmune hepatitis, painting a grim picture of the chronic liver afflictions children face today [1]. Cirrhosis, a hallmark of advanced CLD, manifests as the histological formation of regenerative nodules encased in fibrous bands, a response to persistent liver injury. This transformation leads to the development of portal hypertension and, ultimately, end-stage liver disease [2]. “The cascade of hepatic fibrosis follows liver injury, marked by an accumulation of extracellular matrix (ECM), further compounding the problem. The presence of ECM within the space of Disse distorts hepatic vasculature, diverting portal and arterial blood supply directly into the hepatic outflow, compromising vital exchange between hepatic sinusoids and adjacent liver parenchyma, such as hepatocytes” [3]. This profound structural transformation begets fibrosis and cirrhosis, which lead to intrahepatic vasoconstriction, causing an increase in intrahepatic vascular resistance. Elevated intrahepatic vascular resistance is the genesis of portal hypertension (PHTN) [4]. “Portal hypertension is the critical underlying process that spawns portosystemic collaterals and marks the advent of severe complications, with variceal hemorrhage taking center stage. Astonishingly, nearly 50% of pediatric patients with CLD suffer gastrointestinal bleeding, a grim testament to the destructive power of these conditions” [5]. “Esophageal varices, the harbingers of variceal hemorrhage, progressively develop in approximately 7-8% of patients each year, transitioning from small to large varices at a rate of 10-12% annually” [6]. “Upon the initial diagnosis of liver cirrhosis, esophageal varices make their presence felt in about 40% of patients with compensated disease and a staggering 60% of those with decompensated disease” [7]. The urgency of this matter cannot be overstated, given that variceal hemorrhage is a leading cause of morbidity and mortality among patients grappling with portal hypertension. Therefore, preventing variceal hemorrhage emerges as a paramount concern, necessitating the identification of patients with esophageal varices for primary prophylaxis,

typically involving beta-adrenergic receptor antagonists [8]. While the gold standard for diagnosing and assessing varices remains upper gastrointestinal tract (GIT) endoscopy, this method presents substantial challenges. It is time-consuming, invasive, and carries inherent risks, especially when dealing with children, and it is further complicated by limited access to pediatric endoscopy facilities in many regions [5]. The quest for a reliable, noninvasive alternative becomes evident in light of these obstacles. Noninvasive markers of liver fibrosis, such as Transient elastography, Fib-4, Forns Index, and Lok Score, have shown promise in predicting esophageal varices in cirrhotic patients, given that portal hypertension often arises from increased hepatic resistance due to fibrosis [9]. This study seeks to evaluate and compare the efficacy of esophageal varices in children with CLD of various etiologies. By harnessing these noninvasive tools, we aim to optimize the early detection and prevention of variceal hemorrhage, thus improving the prognosis for these young patients and reducing the burden on healthcare systems. *The study aims to measure laboratory parameters and calculate serum liver fibrosis scores in CLD children.*

METHODOLOGY & MATERIALS

This is a retrospective study; a total of 24 patients were enrolled and analyzed in this study. All patients were diagnosed for esophageal varices in CLD. The study was conducted at the Department of Pediatric Gastroenterology & Nutrition, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. The study duration was two years, from April 2019 to October 2021. Children with chronic liver cirrhosis due to any cause attending the pediatric Gastroenterology & Nutrition department of BSMMU were enrolled in this study. To ensure ethical standards were met, informed consent was obtained from all participating patients, and their personal information was treated with utmost confidentiality. Additionally, the study received approval from the ethical committee at BSMMU, Dhaka, Bangladesh.

Inclusion criteria

- Patients aged under 18 years.
- Patients with Chronic Liver Disease (CLD).

Exclusion criteria:

- Patients with previous or has active gastrointestinal bleeding.
- Patients who previously had undergone injection sclerotherapy, band ligation or surgery for esophageal varices.
- Patients with tense ascites.

Chronic liver disease (CLD) A patient with one or more of the following criteria is considered chronic liver disease. Abnormally dilated submucosal veins in the lower third of the esophagus are called esophageal varices. According to Conn's classification, esophageal varices were classified into 4 grades [10].

Grade-I : Visible only during one phase of respiration/ performance of Valsalva maneuver.
Grade-II : Visible during both phases of respiration.
Grade-III : 3-6 mm in diameter.
Grade-IV : > 6 mm in diameter.

Physical examination was done, and findings (jaundice, hepatomegaly, splenomegaly, ascites) were recorded in the structured questionnaire. Venous blood (about 6 ml) was drawn aseptically for laboratory workup. Alanine aminotransferase, aspartate aminotransferase, total bilirubin, gamma-glutamyl transpeptidase, and serum cholesterol were assessed at the Department of Biochemistry, BSMMU by the auto analyzer, and INR and platelet count was done at the Department of Hematology, BSMMU by the auto analyzer. Then, an endoscopy of upper GIT was done to see the presence or absence of esophageal varices and associated findings using an Olympus video endoscope GIF Q 150 endoscopy machine. A single gastroenterologist of the Pediatric Gastroenterology & Nutrition department of BSMMU had done all endoscopies.

Data analysis

The data collected from the patients were analyzed. The statistical analysis was conducted using SPSS (Statistical Package for the Social Science) version 26 statistical software. The findings of the study were presented by frequency percentage in tables. Median and IQR for continuous variables and frequency distributions for categorical variables were used to describe the characteristics of the total sample. The Chi-square test or Fisher Exact test assessed the association of categorical variables. In the case of skewed data, the Mann-Whitney U test was done to

find the association between continuous data. The diagnostic value of the index was assessed by calculating the area under the receiver operating characteristic (ROC) curves. Diagnostic accuracy was calculated by sensitivity and specificity.

RESULT

Table 1 presents an overview of the demographic characteristics and medical history of the participants in the study. The study population was evenly split, with half of the patients aged 10 years or younger and the other half older than 10. Notably, 79.17% of the cases showed no evidence of consanguinity, while 20.83% indicated the presence of such familial relationships. Additionally, 8.33% of cases had no prior history of jaundice, while 91.67% had a history of jaundice. Moreover, the vast majority (95.83%) had no history of liver disease, while only 4.17% had previously experienced such conditions. Regarding gender distribution, 79.17% of the patients were male, with the remaining 20.83% being female (Figure 1). Table 2 delves into the clinical characteristics of the study participants. It begins by examining the presence or absence of anemia among the individuals. Of the population, 41.67% were free from anemia, while 58.33% exhibited signs of anemia. Additionally, the table addresses the presence of stigmata, with the majority (91.67%) displaying stigmata, while only 8.33% did not exhibit this characteristic. Furthermore, 18 individuals (75.00%) had a palpable liver, while the remaining 25.00% did not. In the case of a palpable spleen, 95.83% of individuals exhibited this characteristic, while only 4.17% did not. Moreover, a considerable number (75.00%) of individuals had ascites, whereas 25.00% did not. Regarding the diagnosis of the study population, half of the patients (50.0%) were diagnosed with Wilson's disease, 16.67% with Chronic hepatitis B, and 12.50% with Autoimmune hepatitis (Table 3). Among the 24 patients with esophageal varices, 20.0% had Grade 1 esophageal varices, 37.5% had Grade 2, 25.0% had Grade 3, and 16.7% had Grade 4 esophageal varices (Figure 2). Table 4 provides a comprehensive overview of essential laboratory parameters and their respective median values and interquartile ranges (IQR). Hemoglobin (Hb) levels had a median value of 10.2 gm/dl, with an IQR ranging from 7.9 to 13.5 gm/dl. Total cell count (TC) was measured at 6300/mm3, with an IQR of 4590 to 9000/mm3. Platelet count, measured in platelets per microliter (/µL) of blood, had a median of 90000/µL and an IQR between 62500 and 133750/µL. Bilirubin levels had a median of 2.7 gm/dl, with an IQR of 1.1 to 5.2 gm/dl. Liver function parameters, including Alanine Transaminase (ALT) and Aspartate Transaminase (AST), were measured in units per liter (U/L). ALT had a median value of 57 U/L, with an IQR of 30.5 to 153.0 U/L, while AST had a median of 134.5 U/L, with an IQR of 78.5 to 210.0 U/L. Gamma-glutamyl transferase (GGT) levels, also measured in U/L, had a median of 132 U/L and an IQR from 85.0 to 245.0 U/L. International Normalized Ratio (INR), a measure of blood clotting, had a median value of 1.6, with an IQR of 1.4 to 1.9. Additionally, the table included Albumin levels in gm/dl, with a median of 25 gm/dl and an IQR of 20.5 to 30.5 gm/dl. Finally, Cholesterol levels, measured in mg/dl, had a median of 105 mg/dl, with an IQR ranging from 90.0 to 140.0 mg/dl. Table 5 offers insights into liver stiffness and serum fibrosis scores for the study population. Liver Stiffness Measurement (LSM) was measured in kilopascals (kPa), with a median value of 13.1 kPa and an IQR range of 10.3-21.6 kPa. Fib-4 had a median value of 1.7, with an IQR of 1.2 to 3.1, indicating the typical range for this index. The Forns Index, with a median of 4.4, exhibited an IQR from 3.9 to 5.7, providing a range within which most Forns Index values in the dataset fell. Lastly, the Lok Score had a median of 0.9, with a narrow IQR from 0.9 to 1.0, indicating limited variability in the Lok Score among the cases examined in the study.

Table 1: Socio-demographical and disease history of the study population (N=24).

Variables	Frequency (n)	Percentage (%)
Age group (in years)		
Up to 10	12	50.00
>10	12	50.00
Consanguinity		
Absent	19	79.17
Present	5	20.83
History of jaundice		
Absent	2	8.33
Present	22	91.67
History of liver disease		
Absent	23	95.83
Present	1	4.17

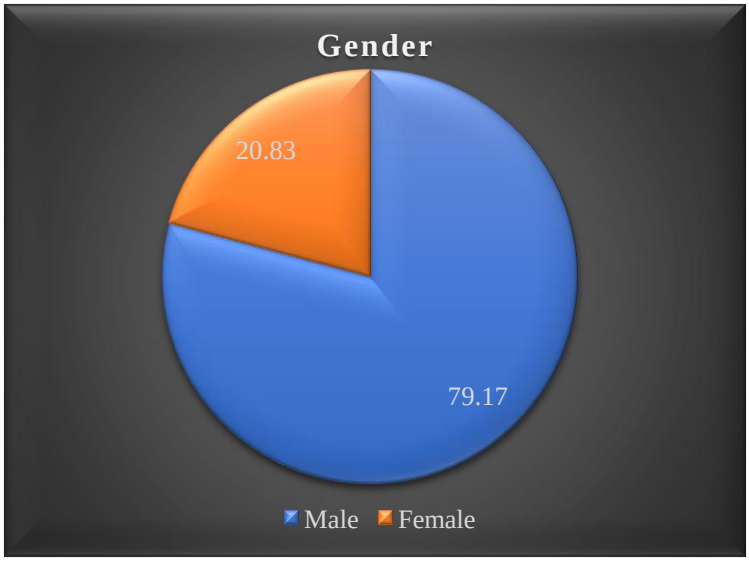

Figure 1: Gender distribution of the study population (N=24).

Table 2: Clinical characteristics of the study population (N=24).

Clinical characteristics	Frequency (n)	Percentage (%)
Anaemia		
Absent	10	41.67
Present	14	58.33
Stigmata		
Absent	2	8.33
Present	22	91.67
Liver		
Palpable	18	75.00
Not palpable	6	25.00
Spleen		
Palpable	23	95.83
Not palpable	1	4.17
Ascites		
Absent	6	25.00
Present	18	75.00

Table 3: Diagnosis of the study population (N=24).

Diagnosis	Frequency (n)	Percentage (%)
Wilson's disease	12	50.00
Biliary cirrhosis	2	8.33
Glycogen storage disease (GSD)	1	4.17
Autoimmune hepatitis	3	12.50
Chronic hepatitis B	4	16.67
Cryptogentic cirrhosis	2	8.33

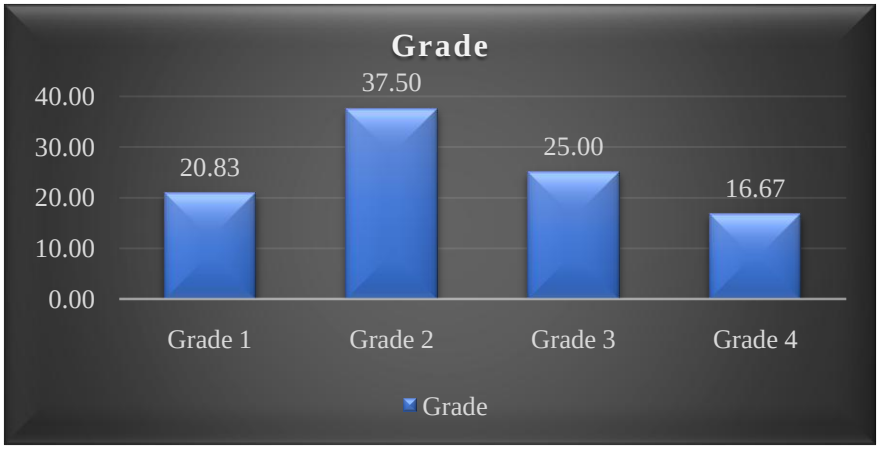

Figure 2: Distribution of patients by grading of esophageal varices (N=24).

Table 4: Laboratory parameters of the studied population (N=24).

Laboratory parameters	Median	IQR
Hb (gm/dl)	10.2	7.9 - 13.5
TC (/mm^3 of blood)	6300	4590 - 9000
Platelet count (/µL)	90000	62500-133750
Bilirubin (gm/dl)	2.7	1.1 - 5.2
ALT (U/L)	57	30.5 - 153.0
AST (UL)	134.5	78.5 - 210.0
GGT (UL)	132	85.0 - 245.0
INR	1.6	1.4 - 1.9
Albumin (gm/dl)	25	20.5 - 30.5
Cholesterol (mg/dl)	105	90.0 - 140.0

Table 5: Liver stiffness and serum fibrosis scores of the study population.

Variables	Median	IQR
LSM (in kPa)	13.1	10.3 - 21.6
Fib-4	1.7	1.2 - 3.1
Forns Index	4.4	3.9 - 5.7
Lok Score	0.9	0.9 - 1.0

DISCUSSION

"Despite advances in diagnosis and treatment, bleeding from esophageal varices is one of the significant causes of morbidity and mortality among cirrhotic patients. Hence, preventing the first episode of Upper digestive hemorrhage (UDH) caused by the rupture of EVs may reduce mortality, morbidity, and healthcare costs. Primary prophylaxis is recommended for high-risk patients who have not bled yet with medium or large-sized EVs. The purpose is to avoid the first episode of digestive hemorrhage. The current therapeutic options include beta-blockers (mainly propranolol) and endoscopic methods, particularly elastic ligation of EVs" [11]. Esophageal varices were found in 71.4% of Bangladeshi children with CLD [12]. In Canada, Gana et al. (2011) found that 69% of studied children had EVs, while in Brazil, Fuguendes et al. (2008) found that 60% had EVs on their first upper GI endoscopy. We found 74.00% of patients with esophageal varices in our study. Of the 24 patients with esophageal varices, 10 (41.7%) had large esophageal varices [13,14]. Other studies found that 32% to 55% of children had large EVs, supporting the present study [13,14]. The majority of the children in the present study were male. Male predominance was also observed in other studies [12,15]. However, Gana et al. (2011) found that most female children in their study. Another study found no gender difference regarding this issue [13,16]. The mean age of the children was 10.7± 4.2 years. Rukunuzzaman (2015) evaluated the clinical and laboratory profile of Wilson's disease (WD) in children, where he found that the mean age of the children was 8.5± 4.5 years. In contrast, Alam et al. (2019) observed that the mean age of children with CLD was 9.7± 3.2 years, comparable to the present study [12,15]. Among the study population, Consanguinity was observed in 5 patients. Consanguinity of marriage is a feature of WD because it is an

autosomal recessive condition. Consanguinity of marriage was found in 30% of patients in the study of Rukunuzzaman (2015) [15]. Tryambak et al. (2009) found WD more prevalent among the children of consanguineous parents in Japan. Stigmata was present in 91.67% of patients. This study found that 75.0% of patients had palpable liver. This finding was consistent with other studies [5,12,13,17]. Half of the patients were diagnosed with Wilson's disease, 4(16.67%) with Chronic hepatitis B, and 3(12.50%) were diagnosed with Autoimmune hepatitis. The prospective study of Alam et al. (2019) reported that "the predominant etiology of CLD was Wilson's disease (65.5%); other causes included chronic hepatitis B (6%), autoimmune hepatitis (7.1%), biliary atresia (6%), celiac disease associated liver disease (1.2%), glycogen storage disease (1.2%), hepatitis C virus infection (1.2%), and cryptogenic (11.9%)". The present study did not find any patients with biliary atresia, which might be due to the small size of the sample of the present study [12]. A limited number of pediatric and most adult studies showed similar results. Fuguendes et al. (2008), in a study of 85 children and adolescents with cirrhosis, showed that patients having a platelet count <1,20,000/mm3 were more prone to developing EVs (p=0.027) [12-14,18-20]. Another pediatric study from Brazil also found a low platelet count an independent predictor for the presence of EVs with high specificity (88.2%) and positive predictive value (PPV) (86.6%), which is consistent with our findings (specificity 95.6%, PPV 96.2%) for the presence of varices [21]. Gana et al. (2011) also found a low platelet count (<1,15,000/ mm3) in children having EVs on a univariate model [13]. A recent pilot study in adults from India also showed the platelet count <1,50,000/mm3 as the single best independent predictor of EVs in newly diagnosed CLD with high sensitivity (82.05%) and specificity (81.82%) [22]. Another study in adults from Nepal also found similar results [23]. The median bilirubin count of children with EVs (2.7 gm/dl). This matched the studies of Fuguendes et al. (2008) and Adami et al. (2013) [5,14]. The median Liver Stiffness Measurement (LSM), Fib-4, Forns Index, and Lok score were 13.1 kPa, 1.7, 3.1, and 0.9 in children with EVs. Transient elastography (Fibroscan) is an ultrasound technique that uses pulse-echo ultrasound acquisitions to measure liver stiffness. The use of Fibroscan in patients with liver disease is based on the assumption that fibrosis results in increased stiffness of the liver parenchyma. Since fibrosis is one of the significant determinants of portal hypertension, assessing the relationship between liver stiffness and portal pressure makes sense [11]. In the current study, Liver Stiffness Measurement could predict esophageal varices at a cut-off value of 8.25 kPa with 83.3% sensitivity and 75.0% specificity.

Limitations of the study: Every hospital-based study has limitations, and the present study is no exception. The limitations of the present study are mentioned. Firstly, the sample size may be limited, affecting the generalizability of findings. Additionally, the study's retrospective nature could introduce recall and selection biases. The accuracy of diagnosing esophageal varices might also be influenced by interobserver variability. Furthermore, the study may not account for confounding factors such as comorbidities or medication use. Long-term outcomes and treatment efficacy should be explored, limiting the comprehensive understanding of CLD management in pediatric populations. Future prospective research with larger cohorts is needed to address these limitations.

CONCLUSION AND RECOMMENDATIONS

In conclusion, our study on "The Assessment of Chronic Liver Disease (CLD) Based on Esophageal Varices in Children" sheds light on a critical aspect of pediatric hepatology. The findings of this research underscore the significance of early detection and management of esophageal varices in children with chronic liver disease, as they serve as valuable prognostic indicators and offer insights into the severity of underlying liver conditions. Our investigation revealed that the presence of esophageal varices in pediatric CLD patients is associated with a heightened risk of complications such as bleeding, which can be life-threatening. As a result, regular screening and monitoring of these patients for the development of varices should be an integral part of their clinical care. Furthermore, our study underscores the importance of a multidisciplinary approach involving pediatric gastroenterologists, hepatologists, and other healthcare providers in the comprehensive management of pediatric CLD. Early intervention and appropriate medical strategies, including variceal banding or pharmacological therapy, can mitigate the risk of bleeding and improve overall patient outcomes. In essence, our research emphasizes the necessity of early assessment and intervention in children with CLD to prevent the progression of liver disease and its associated complications, ultimately improving the quality of life and long-term prognosis for these young patients. Further studies are warranted to refine our understanding of this complex clinical scenario and to develop more targeted interventions for this vulnerable population.

Ethical approval: The study was approved by the Institutional Ethics Committee.

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