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Blood Ammonia Concentration in Children with Chronic Liver Disease: A Tool for Prediction of Esophageal Varices

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Esophageal varices (EVs) are a serious complication of portal hypertension in patient with chronic liver disease (CLD). The major portion of ammonia carried by portal blood is shunted into systemic circulation in chronic liver disease. The upper GI endoscopy is currently the best reliable method to diagnose the presence of esophageal varices. But it is invasive, relatively expensive and not easily available. Blood ammonia is a noninvasive and easily accessible laboratory parameter that can predict the presence of esophageal varices.

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Objectives: To observe the blood ammonia concentration in children with chronic liver disease: a tool for prediction of esophageal varices.
Methods: This cross sectional observational study was conducted at the Department of Paediatric Gastroenterology and Nutrition, BSMMU, Dhaka, Bangladesh from January 2018 to December 2019. A total of 63 cases of CLD were selected. Study sample were selected according to the inclusion and exclusion criteria. Along with proper clinical history, examination & initial investigation, fasting venous blood ammonia level and upper GI endoscopy were done in all patients. Receiver-Operator Characteristic (ROC) curve was analysis to set up a cut-off value of blood ammonia for prediction of esophageal varices. Sensivity, specificity, positive predictive value, negative predictive value and accuracy were determined to see the performance of blood ammonia value as a diagnostic test for esophageal varices.
Results: Among the 63 patients, (74.6%) had esophageal varices. Wilson disease was the most common etiology of CLD (43; 68.3%) among the studied patients. The mean blood ammonia level were 40.5± 18.0 (µmol/L), 50.5± 14.3 (µmol/L), 50.7± 9.9 (µmol/L), 53.1± 26.9 (µmol/L) and 71.9± 19.0 (µmol/L) in absent esophageal varices, grade-I, grade-II, grade-III and grade-IV esophageal varices respectively. The difference was statistically significant (<0.05). Moderate correlation (r= 0.452; p value = 0.001) between blood ammonia level and grades of esophageal varices was found. It was observed that wasting of thenar and hypothenar muscle was the most common stigmata, seen in 15 (23.8%) cases, 2 (3.2%) had clubbing, 7 (11.1%) had leuconychia, 1 (1.6%) had palmer erythema, 3 (4.8%) had gynacomasia and 1 (1.6%) had testicular atrophy. Wilson disease was the most common 43 (68.3%). It was observed that 45 (71.4 %) patients had raised serum ALT and 45 (71.4%) had low serum albumin (<3.5 g/dl). Low haemoglobin (<9 gm/dl) was found in 47 (74.6%) cases, raised serum bilirubin level (>1.2 mg/dl) in 29 (46.03%) cases, thrombocytopenia (platelet count $<1.50\times10^9/mm^3$) in 36 (57.1%) patients and prolonged INR (>1.5) in 29 (46.03%) cases, blood ammonia was raised (>32 µmol/L) in 52 (82.5%) cases. It was observed that the mean ± SD blood ammonia level was 56.2± 17.9 µmol/L in esophageal varices present group (n = 47) and 40.5± 18.0 µmol/L in absent esophageal varices group (n = 16). Here p value is 0.004, which is statistically significant.
Conclusion: Blood ammonia concentration is a biochemical predictor for assessing the grading of esophageal varices. In the present study, a moderate positive correlation was found between blood ammonia concentration and grades of esophageal varices in children with CLD.

Keywords: Blood ammonia level; esophageal varices; chronic liver disease.

1. INTRODUCTION

Chronic liver disease (CLD) is common among paediatric population. Cirrhosis is considered to be the most advanced stage of CLD. Several complications are related to advanced liver disease. Esophageal variceal bleeding is one of the most dreadful complication of CLD because of its high mortality. When the CLD is diagnosed for the first time, esophageal varices are present in about 40% of patients with compensated disease and in about 60% patients with decompensated disease [1]. Portal hypertension may manifest as gastrointestinal bleeding and splenomegaly [2]. The incidence of esophageal varices increases in approximately 5% per year in patients with CLD and the rate of progression from small to large varices is approximately 5–10 % per year [3]. Increasing in size of varices is associated with an increase in variceal wall tension to a critical level at which varices rupture and cause life threatening bleeding. Annual incidence of gastrointestinal hemorrhage is 5% in those with small esophageal varices and 15-20% in patient with large esophageal varices [1]. Chance of rebleeding are 26% and 15% death by 30 days after initial episode of variceal bleeding [4]. Patients following variceal bleeding, the mortality rates of 6 weeks, 1 year and over all are 18.4%, 32.6% and 48.2% respectively [5]. Hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome are the devastating complications of chronic liver disease and usually results from gastrointestinal bleeding [6]. Therefore early diagnosis, proper management and regular follow ups are essential. Thus variceal bleeding prevention is an important factor for the patient as well as for the physician dealing with them. The first step of this prevention is to identify the patient at risk of bleeding and to select them for prophylactic treatment with beta adrenergic receptor antagonists to reduce the incidence of variceal bleeding [7]. American College of

Gastroenterology recommends screening all CLD patients for the presence of esophageal varices and treating patients with large varices with beta blockers to reduce the incidence of first variceal bleeding. Therapies of portal hypertension are aimed mainly at trying to manage and reduce the complication. This may be achieved with pharmacological agents, therapeutic endoscopy, interventional radiology or surgery [8]. The direct way for the diagnosis of portal hypertension is direct measurement of portal pressure or hepatic venous pressure gradient [9]. These measurements can be obtained only by invasive methods, which are not feasible in most centers of the world. The indirect way to assess portal hypertension is by detection of esophageal varices. There are a number of ways to assess the status of esophageal varices, these are barium swallow of esophagus, ultrasonography and upper gastrointestinal endoscopy. The upper gastrointestinal endoscopy is currently the best reliable way to diagnose esophageal varices [9]. "Therefore performing an upper GI endoscopy for identification of varices in all CLD patients implies a large number of unnecessary endoscopies. Thus subsequently increases the workload of endoscopy units as well as an economic burden to the patients and this is more difficult in a resource limited country like ours. It would be beneficial patients with higher chances of esophageal varices could be diagnosed by of non-endoscopic, non-invasive methods that can accurately predict esophageal varices and thereby reduce the necessity of endoscopic screening. In chronic liver disease, the major portion of ammonia carried by portal blood is shunted by portosystemic collaterals into systemic circulation. The raised blood ammonia level may be an indicator of the presence of esophageal varices. The generated ammonia, which reaches the liver through the portal vein, is converted to urea by means of urea cycle and excreted from the kidneys. In patients with decreased hepatic functional reserve or those with portosystemic shunt, ammonia level in the blood rises [10]. Blood ammonia could be a good mirror of portosystemic collaterals in CLD patients [11]. On the other hand, a recent study found that there was a moderate but significant correlation between blood ammonia level and size of esophageal varices" [12]. No such study has been conducted in Banglasesh to see the correlation between blood ammonia level and esophageal varices in CLD children. Therefore, this study has been undertaken to observe the correlation between blood ammonia level and esophageal varices.

2. MATERIALS AND METHODS

This cross sectional observational study was conducted at the Department of Paediatric Gastroenterology and Nutrition, BSMMU, Dhaka, Bangladesh from January 2018 to December 2019. A total of 63 cases of CLD were selected. Study sample were selected according to the inclusion and exclusion criteria. Along with proper clinical history, examination & initial investigation, fasting venous blood ammonia level and upper GI endoscopy were done in all patients.

Inclusion criteria:

- Children of either gender (aged < 18 years) diagnosed as chronic liver disease as per operational definition.

Exclusion criteria:

- Active or recent (within 2 weeks) upper GI bleeding.
- Patient on beta blocker therapy.
- Endoscopic sclerotherapy or band ligation done for esophageal varices.
- Previous surgery for portal hypertension.

Operational definitions:

Chronic liver disease (CLD): A patient having any one or more of the following criteria were considered as CLD.

- Jaundice or raised ALT with any stigmata of CLD (Palmer erythema, clubbing, leukonychia, thenar and/ or hypothenar wasting, spider angioma, gynaecomastia, Dupuytren's contracture, etc.)
- Presence of jaundice for a long period (>6 months) with elevated ALT
- Those diseases which are chronic in nature like Wilson's disease, autoimmune hepatitis, Alfa 1 antitrypsin deficiency, etc.
- Histologically diagnosed as a case of chronic hepatitis or cirrhosis [13].

Portal Hypertension: Elevation of the portal venous pressure above the normal level is called portal hypertension. It is clinically evident by presence of splenomegaly and/or gastrointertinal

tract bleeding and endoscopically evident by presence of esophageal varices [9].

Esophageal varices:

- Esophageal varices were classified in to 4 grades [14].
- Grade-I - Visible only during one phase of respiration/performance of Valsalva manoeuvre.
- Grade-II- Visible during both phases of respiration.
- Grade-III- 3–6 mm in diameter.
- Grade- IV- >6mm in diameter.

Medium varices:

- Grade- I and grade- II.

Large varices:

- Grade III and grade IV [12].

Study procedure:

- Patients attending Pediatric Gastroenterology & Nutrition department having chronic liver disease will initially be enrolled for the study.
- Study protocol was approved by Institutional Review Board (IRB) of BSMMU.
- During the study period, patients were admitted at the Department of Paediatric Gastroenterology and nutrition. By method of exclusion 63 cases were included in this study regardless of sex and cause of chronic liver disease.
- A standard questionnaire was designed with a view to collect data from the respondents.
- Initial evaluation by history and clinical examination of the patients were done and recorded in the preformed data collection sheet by the researcher herself.
- Laboratory method:
- CBC and INR were done by auto analyzer at Hematology Department. Serum ALT, serum albumin and other biochemical tests were done at Biochemistry Department by auto analyzer.
- Ultrasonography was done at Radiology and imaging Department by afiniti 70G apparatus equipped with 3.5 MHz transducer.
- Blood collection and measurement of blood ammonia level:
- Fasting venous blood (about 5 ml) will be drawn aseptically for blood ammonia level. Blood was collected into an EDTA evacuated tube without using tourniquate. The samples will be immediately carried to laboratory gently in an icebox and analyzed within 30 minutes of arrival. Blood ammonia level was assessed at Biochemistry department of BSMMU using by Abbot Architect plus ci4100 machine by auto analyzer. Result of the investigations were collected and recorded in structured questionnaire.
- Endoscopy of Upper GIT:
- Then endoscopy of upper gastrointestinal tract was done by a single Paediatric Gastroenterologist at department of Paediatric Gastroenterology. Olympus CV-150 video endoscope (Olympus, Japan) was used in all cases. Premedication, comprising of topical pharyngeal anaesthesia with lidocain spray was given before the procedure.
- **Esophagus** was carefully surveyed during endoscopy for Evidence of esophageal varices, Size of the varices, Esophageal varices were classified in to 4 grades according to Conn's classification. Endoscopy machine will be carefully cleaned & disinfected by emerging the scope in 2% gluteraldehyde for 20 minutes & then will be washed with clean water.

Data processing and analysis: All the data were entered into a personal computer and thoroughly checked for any possible errors and then processed and analyzed by Statistical Package for Social Science (SPSS 22.0 Chicago, Illinois, 2016). Frequency was analyzed by mean, range, percentage for categorical variables: age, sex, clinical features, blood ammonia concentration and grading of esophageal varices. Unpaired t-test was applied to compare the proportion between blood ammonia concentration and endoscopy findings. Correlation analysis between blood ammonia values and grades of esophageal varices were done by "Spearman's rank order correlation coefficient" and corresponding 'p' value was analyzed. Correlation coefficient 'r' value between 0.1 to 0.3 was considered as weak correlation, between 0.4 to 0.6 as moderate and 0.7 to 1 as strong correlation. 'p' value of <0.05 was taken as statistically significant. Receiver Operator Characteristics Curve was analyzed to set up a cut-off value. Sensitivity, specificity, positive predictive value, negative predictive

value and accuracy were also determined to see performance of blood ammonia concentration value as a diagnostic test for esophageal varices [12].

3. RESULT

Age distribution of the studied patients: A total of 63 cases were included in this study. It was observed that almost half, 31 (49.2%) of cases belonged to age group of 6-10 years followed by 25 (39.7%) patients who belonged to age group of 11-18 years and 7 (11.1%) patients were ≤5 years age group. Among 63 patients 36 (57.1%) were male and 27 (42.9%) were female (Table 1).

Table 1. Age distribution of the studied patients (n=63)

Age (in years)	Number	Percent
≤5	7	11.1
6-10	31	49.2
11-18	25	39.7
Sex		
Male	36	57.1%
Female	27	42.9%

Physical findings of the studied patients (n=63): Fig. 1 shows the clinical features of the studied patients. It was observed that majority, 54 (85.6%) patients had anaemia, 40 (63.5%) had splenomagaly, 39 (61.9%) had ascites. Among the other features jaundice was present in 32 (50.8%), hepatomegaly in 29 (46.0%) and stigmata of CLD in 19 (30.2%) patients.

Stigmata of CLD in studied patients (n=63): Fig. 2 shows the stigmata of CLD in studied patients. It was observed that wasting of thenar and hypothenar muscle was the most common stigmata, seen in 15 (23.8%) cases, 2 (3.2%) had clubbing, 7 (11.1%) had leuconychia, 1 (1.6%) had palmer erythema, 3 (4.8%) had gynacomasia and 1 (1.6%) had testicular atrophy.

Etiology of CLD in studied patients (n=63): Fig. 3 shows the etiology of CLD in studied patients. Wilson disease was the most common 43 (68.3%). Twelve (19.0%) patients were Cryptogenic, two (3.2%) were storage and one (1.6%) were billiary cirrhosis. There were 3 (4.8%) cases of Hepatitis B virus, 1 (1.6%) of Hepatitis C virus and 1 (1.6%) of autoimmumo hepatitis.

Table 2 shows the laboratory parameters of studied patients. It was observed that 45 (71.4 %) patients had raised serum ALT and 45 (71.4%) had low serum albumin (<3.5 g/dl). Low haemoglobin (<9 gm/dl) was found in 47 (74.6%) cases, raised serum bilirubin level (>1.2 mg/dl) in 29 (46.03%) cases, thrombocytopenia (platelet count $<1.50\times10^9/mm^3$) in 36 (57.1%) patients and prolonged INR (>1.5) in 29 (46.03%) cases, blood ammonia was raised (>32 µmol/L) in 52 (82.5%) cases.

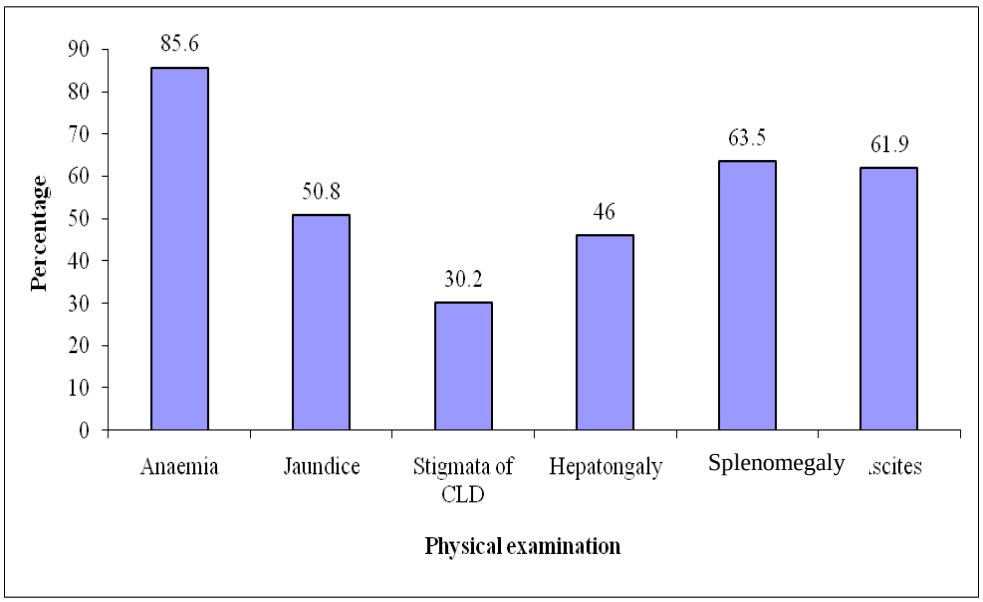

Fig. 1. Physical findings of the studied patients (n = 63)

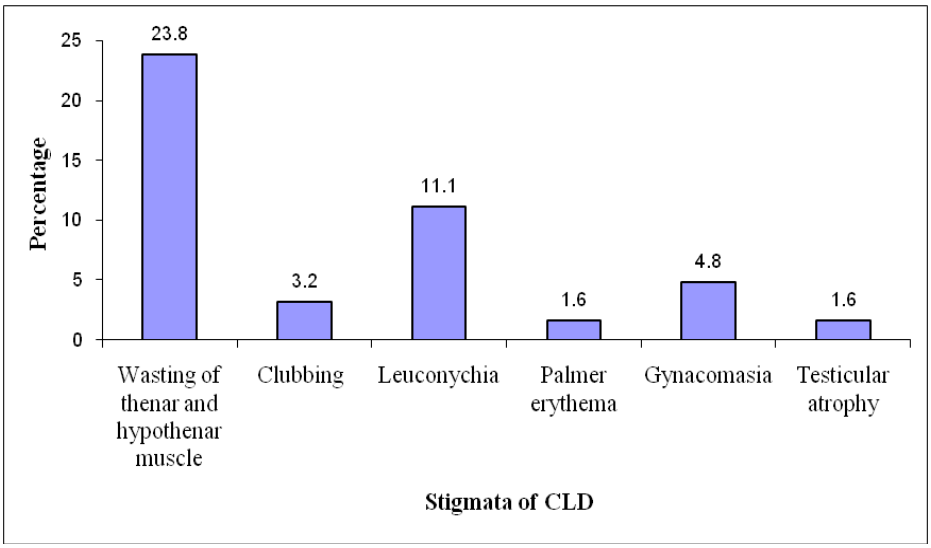

Fig. 2. Stigmata of CLD in studied patients (n=63)

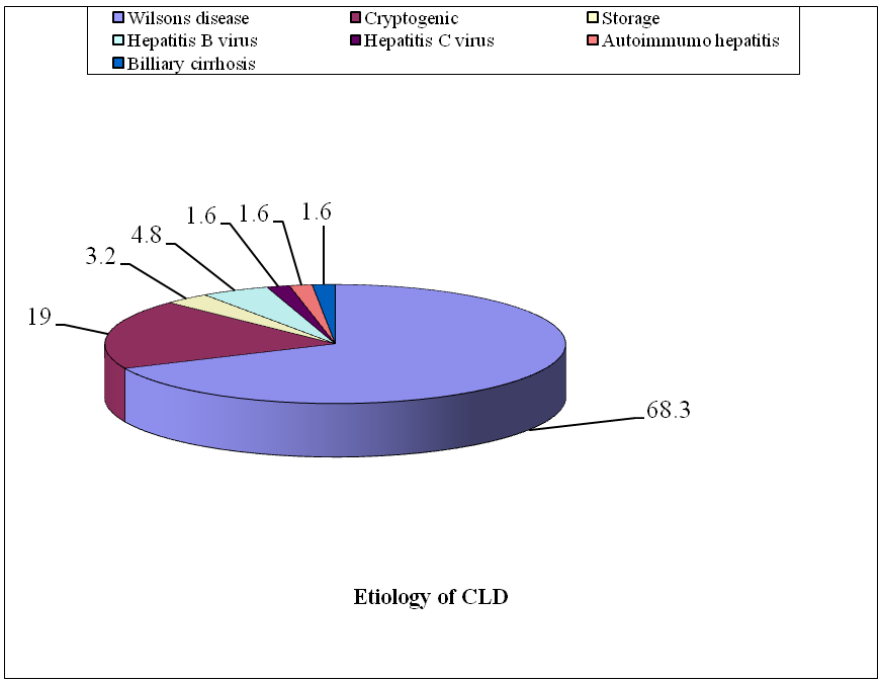

Fig. 3. Etiology of CLD in studied patients (n=63)

Table 2. Distribution of the studied patients by laboratory test (n=63)

Laboratory test	Number (%)	Mean ± SD	Range
Hb (<9 gm/dl)	47 (74.6)	7.4±2	3.7- 8.9
TC (<4000 /mm^3)	12 (19.0)	2720.8± 644.3	1200- 3500
Platelet (< $1.50x10^9 mm^3$)	36 (57.1)	1.03± 1.2	0.5- 1.47
Serum bilirubin (>1.2 mg/ dl)	29 (46.0)	6.05± 5.4	2.1- 28.8
Serum ALT (>40 U/L)	45 (71.4)	125.25± 102.5	45- 657
INR (>1.5)	29 (46.3)	3.2± 2.5	1.7- 14.36
Serum albumin (<3.5 gm/ dl)	45 (71.4)	2.23± 0.6	1.1- 3.5
Blood ammonia (>32 µmol/ L)	52 (82.5)	56.7± 18.8	33- 113

Table 3. Distribution of the studied patients by upper Gastrointestinal Tract Endoscopy (n=63)

Endoscopy of upper GIT	Number	Percent
Esophageal varix		
Absent	16	25.4
Grade-1	6	9.5
Grade-2	19	30.2
Grade-3	12	19.0
Grade-4	10	15.9
Fundal varix	1	1.6
Gastropathy	2	3.2

It was observed that among 63 patients, 47 (74.6%) patients had esophageal varices. Grade I varices was found in 6 (9.5%) patients, 19 (30.2%) patients had grade II esophageal varices, 12 (19.0%) had grade III and 10 (15.9%) had grade IV varices. Sixteen (25.4%) patients did not have any varix. Gastropathy was seen in 2 (3.2%) patients and fundal varix was found in 1 (1.6%) patients (Table 3).

It was observed that the mean ± SD blood ammonia level was 56.2± 17.9 µmol/L in esophageal varices present group (n = 47) and 40.5± 18.0 µmol/L in absent esophageal varices group (n = 16). Here p value is 0.004, which is statistically significant (Table 4).

4. DISCUSSION

Chronic liver disease (CLD) is common among pediatric population. When CLD is diagnosed for the first time esophageal varices are present in about 40% of patients with compensated disease [1]. Portal hypertension is the hemodynamic abnormality frequently associated with serious liver disease. It is estimated that approximately 50% of pediatric patients with chronic liver disease will experience gastrointestinal bleeding" [15]. Increasing in size of varices is associated with an increase in variceal wall tension to a critical level at which varices rupture and cause life threatening bleeding. Annual incidence of gastrointestinal hemorrhage is 5% in those with small esophageal varices and 15-20 % in patient with large esophageal varices [1]. Esophago-gastro-duodenoscopy is required to detect the gastro esophageal varices. But the procedure is invasive, painful to the patient and is not available in all centres. In chronic liver disease, the major portion of ammonia carried by portal blood is shunted by portosystemic collaterals into systemic circulation. The raised blood ammonia level may be an indicator of the presence of esophageal varices. A total of 63 patients with CLD were included in this study. They were between 1.5 to 18 years age range. Most, 31 (49.2%) of the patients were in the age group between 6-10 years. In another study done in BSMMU" (Hussain et al., [16] showed "48% of cases were between 6 to 18 years age group. In present study, male were 57.1% and female 42.9%". Similar results were also observed in another study done in Bangladesh by Karim et al [17]. In his study 31 (56%) were male and 24 (44%) female. Hussain et al., [16] showed male (75%) and female (25%). This male prepondence results from under reporting of symptoms in female patient due to gender biasness of the parents. History of hematemesis and melena were found in 10 (15.9%) and 11 (17.5%) patients respectively. Hossen et al. [18] found 3 (10%) cases had history of hematemesis and 3 (10%) cases of history of melena. Fourteen (22.2%) patients had family history of liver disease in this study and similar result was found by Karim et al.,[19] where positive family history was in 21% cases. Fifteen (23.8%) patients had parental consanguinity and these were Wilson disease cases. Karim et al.,[19] found similarly parental consanguinity in 24% cases and all were Wilson disease. Rukunuzzaman et al.,[20] also found positive family history in 15% and parental consanguinity in 30% cases of Wilson disease. In present study Wilson disease was the most common 43(68.3%) etiology of CLD. Only 15 (23.8%) patients had parental consanguinity, rest 44.5% had no parental consanguinity. Regarding clinical feature, anaemia 54 (85.6%) and splenomegaly 40 (63.5%) were the two most common presenting features followed by ascites 39 (61.9%), jaundice 32 (50.8%), hepatomegaly 29 (46.0%) and stigmata of CLD 19 (30.2%). Allan et al. [21] and Kumar et al. (2013)[22] demonstrated similar clinical findings in their studies. Karim et al. [17] found hepatomegalyas the commonest (78.4%) presenting sign. Most common etiology of chronic liver disease was found to be Wilson disease (68.3%). Alam el al.,[23] found similar results in a study done at BSMMU. The predominant etiology of CLD was

Table 4. Distribution of the blood ammonia level with esophageal varices (N=63)

Varices	Blood ammonia (µmol/L)			p value
	n	Mean± SD	Range	
Present	47	56.2± 17.9	23- 113	0.004[s]
Absent	16	40.5± 18.0	27- 98	

s= significant, Result was expressed as Mean± SD, Statistical analysis by Unpaired t-test was done as a test of significance, p value was significant (<0.5)

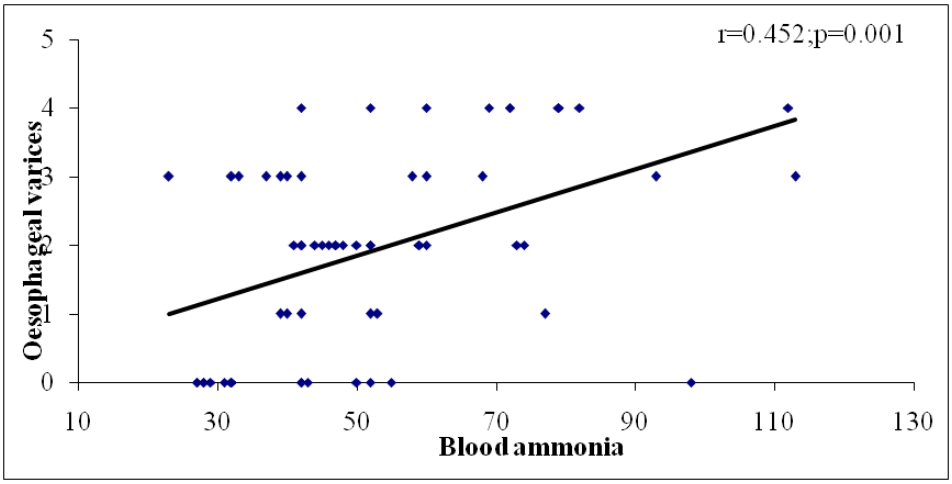

Fig. 4. Graph showing regression analysis results

Wilson disease (n = 55, 65.5%). Alam et al., [23] found infective cause was the most common cause of CLD in a study done in Dhaka Shishu Hospital. It was observed that the pattern of etiology is regionally variable. Higher frequency of Wilson disease may be due to availability of diagnostic tool of Wilson disease and referral of Wilsonian patient from different part of our country. But as our institution is the tertiary care centre it may not reflect the true scenario of whole country. Thrombocytopenia is a noninvasive predictor of esophageal varices. In the present study platelet count of $<1.50\times10^9/mm^3$was found in 57.1% of cases and mean ± SD platelet count was 1.03± $12\times10^9/mm^3$. Thrombocytopenia occurs due to disease itself, hypersplenism and drug (eg. penicillamine). In studies of Farooqi et al.,[24] and Zein et al.,[25] also found thrombocytopenia, which were associated with esophageal varices. Our study findings were similar with that of other studies. In this study low serum albumin (<3.5 g/dl) was found in 71.4 % cases. Sarwar et al.,[26] and Schepis et al. [27] found similar finding in their studies. In this study, upper GIT endoscopy showed 47 (74.6%) patients had esophageal varices and 16 (25.4%) cases had no esophageal varix. This is in consistent withstudies of Das et al., [28], Demirel et al.,[29], Alam et al.,[23] and Prabakaran et al.[30] who found 87%, 91%, 86% and 93.5% cases of esophageal varices in their studies respectively. In this study 6 (9.5%) cases had grade I, 19 (30.2%) cases had grade II, 12 (19.0%) cases grade III, and 10 (15.9%) cases had grade IV esophageal varices. In the present study gastric varices and portal hypertensive gastropathy was found in 1.6% and 3.2 % cases respectively. Fagundes et al. [31] found fundal varices in 19% cases. In another study gastropathy was diagnosed in 58.8% cases [32]. We have found gastropathy only in few patients because it may develop later in the course of disease.

5. CONCLUSION AND RECOMMENDA-TION

Blood ammonia concentration is a biochemical predictor for assessing the grading of esophageal varices. In the present study, a moderate positive correlation was found between blood ammonia concentration and grades of esophageal varices in children with CLD. It can be concluded that high blood ammonia level denotes higher chances of presence of esophageal varices and this simple, low cost, minimally invasive test can serve as an effective diagnostic tool for diagnosis of esophageal

varices in children with CLD. This may guide the paediatricians in descision making for further evaluation, prophylactic management and prevention of life threatening complications. However, this needs prospective study with a large number of patients for more acurate prediction prior to recommend it.

6. LIMITATIONS OF THE STUDY

1. Times and resources were limited.
2. Small sample size.
3. This study was carried out in a specialized tertiary care hospital which perhaps not the true representation of all Bangladeshi children having portal hypertension.

CONSENT

As per international standard or university standard, patient (s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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