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Correlation between Blood Ammonia Level and Grading of Esophageal Varices in CLD Patients

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Abstract **Original Research Article**

Introduction: Chronic liver disease is an important cause of morbidity and mortality in Bangladeshi children. Development of esophageal varices and bleeding is one of the major complications of CLD. The mortality from each episode of variceal bleeding is 30-50% depending on the clinical status of the patient. The upper GI endoscopy is currently the best reliable method available to diagnose the presence of esophageal varices. ***Objective:*** To Assess the correlation between blood ammonia level and grading of esophageal varices in CLD patients. ***Methods:*** This cross sectional observational study was conducted at the Department of Paediatric Gastroenterology and Nutrition, BSMMU, Dhaka 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. Among the studied patient, the mean ± SD blood ammonia level was 40.5± 18.0 µmol/L in absent esophageal varices group, 50.5± 14.3 µmol/L in grade I varices group, 50.7± 9.9 µmol/L in grade II esophageal varices group, 53.1± 26.9 µmol/L in grade III varices group and 71.9± 19.0 µmol/L in grade IV esophageal varices group. Here p value is 0.002, which is statistically significant. 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. It was observed that the mean ± SD blood ammonia level was (50.7± 10.8) µmol/L in medium esophageal varices group (n = 25) and (61.7± 21.0) µmol/L in large esophageal varices group (n = 22) . Here p value is 0.026, which is statistically significant. Spearman's rank order correlation analysis shows moderate positive correlation between blood ammonia concentration and grades of esophageal varices (r= 0.452) and corresponding p value was 0.001 which is statistically significant. The receiver-operator characteristic (ROC) curves for prediction of medium varices are depicted in table VI. Based on the receiver-operator characteristic (ROC) curves blood ammonia had area under curve 0.765. Receiver-operator characteristic (ROC) was constructed by using blood ammonia, which gave a cut off value of 39.5 (umol/L), with 96.0% sensitivity and 56.2% specificity for prediction of medium varices. It was observed that 31 (75.6%) patients had positive blood ammonia level (>39.5 umol/L), among them 24 patients had medium varices and 7 patients had no medium varices. Ten (24.4%) patients had negative (≤39.5 umol/L) blood ammonia level, among them 1 patient had medium varices and 9 patients had no medium varices. Sensitivity of blood ammonia was found to be 96.0%,

specificity 56.3%, positive predictive value 77.4%, negative predictive value 90.0% and accuracy 80.5%. Twenty four (63.2%) patients had negative (≤56.5 umol/L) blood ammonia level, among them 9 patients had large varices and 15 patients had no large varices. Sensitivity of blood ammonia was found to be 59.1%, specificity 93.8%, positive predictive value 92.9%, negative predictive value 62.5% and accuracy 73.7%. ***Conclusion***: From this study it may be concluded that blood ammonia level positively correlates with the grades of esophageal varices in children with chronic liver disease.

Keywords: Esophageal Varices, Chronic Liver Disease, Blood Ammonia Level.

INTRODUCTION

Chronic liver disease is an important cause of morbidity and mortality in Bangladeshi children. Development of esophageal varices and bleeding is one of the major complications of CLD. The mortality from each episode of variceal bleeding is 30-50% depending on the clinical status of the patient. The upper GI endoscopy is currently the best reliable method available to diagnose the presence of esophageal varices. 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]. Liver diseases persisting for many years without progressive improvement back to normal liver are called chronic liver disease [3]. It is a disease process of the liver that involves a process of progressive destruction and regeneration of the liver parenchyma leading to fibrosis and cirrhosis (chronic liver disease – Wikipedia, 2018). Chronic hepatitis and cirrhosis of liver are the two entities that are included in CLD [3]. Sometimes it is said that the duration of disease have to be >6 month. But it can be misleading as many diseases like Wilson's disease, autoimmune hepatitis, metabolic disorders are considered as CLD at first contact and if left untreated they can produce several complications. Thus this 6 months cut off is applicable for hepatitis B infection [4]. 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 [5]. 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 [6]. Blood ammonia could be a good mirror of portosystemic collaterals in CLD patients [7]. However, endoscopy is costly and is a invasive procedure. Moreover facility for endoscopy is not available in all centers, even in most of tertiary health care facilities of Bangladesh till now. Performing endoscopy in children is terrifying and difficult because of non-co-operative nature of the patient. 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 if 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. There is no such studies has yet been undertaken to observe the relation between blood ammonia concentration and esophageal varices in paediatric population of Bangladesh. This study will encourage the paediatritians to use blood ammonia as an indirect parameter which will indicate the presence and severity of esophageal varices. Determining the relation between blood ammonia level and esophageal varices will help to initiate early prophylactic treatment and to prevent catastrophic event like variceal bleeding, morbidity and mortality risk and thereby reduce the necessity of endoscopic screening.

MATERIALS AND METHODS

Type of Study:

Cross sectional observational study.

Place of Study:

Department of Paediatric Gastroenterology & Nutrition, BSMMU, Dhaka, Bangladesh.

Period of Study:

January, 2018 to December, 2019.

Study Population:

Children with chronic liver disease attending the Paediatric Gastroenterology & Nutrition Department of BSMMU, Dhaka, Bangladesh.

Sample Size:

Sample size was calculated using following formula:

$$N = (Za+Zb/ C)^2 + 3$$

So sample size of this study is according to the formula = 63 patients.

Due to limitation of time and resource, all consecutive patients attended in Department of

Paediatric Gastroenterology, BSMMU during the study period will be the cases.

Sampling Procedure:

Sample was collected purposively among children presenting with chronic liver disease due to variable causes attending BSMMU hospital seeking medical advice.

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.

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.

a. 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 [8].

RESULT

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. 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. The most common stigmata, seen in 15 (23.8%) cases and 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-1: Etiology of CLD in studied patients (n=63)

Etiology of CLD	N	%
Wilson Disease	43	68.3%
Cryptogenic	12	19.0%
Storage	02	3.2%
Billiary Cirrhosis	01	1.6%
Hepatitis B Virus	03	4.8%
Hepatitis C Virus	01	1.6%
Autoimmumo Hepatitis	01	1.6%

Table-2: Distribution of the blood ammonia level with different grades of esophageal varices (N=63)

Esophageal varix	Blood ammonia (µmol/L)		p value
	Mean± SD	Range	
Absent	40.5± 18.0	27-98	0.002[s]
Grade-1	50.5±14.3	39-77	
Grade-2	50.7± 9.9	41-74	
Grade-3	53.1± 26.9	23-113	
Grade-4	71.9± 19.0	42-112	
F value	4.718		
DF	4,58		

s= significant
Result was expressed as Mean± SD
Statistical analysis by ANOVA was done as a test of significance
P value was significant (<0.05)

It was observed that among the studied patient, the mean ± SD blood ammonia level was 40.5± 18.0 µmol/L in absent esophageal varices group, 50.5± 14.3 µmol/L in grade I varices group, 50.7± 9.9 µmol/L in grade II esophageal varices group, 53.1± 26.9 µmol/L in grade III varices group and 71.9± 19.0 µmol/L in grade IV esophageal varices group. Here p value is 0.002, which is statistically significant.

Table-3: 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)

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: Distribution of the blood ammonia level with esophageal varices (N=47)

Varices	Blood ammonia (µmol/L)			P value
	N	Mean± SD	Range	
Medium varices	25	50.7± 10.8	39-77	0.026[s]
Large varices	22	61.7± 21.0	23-113	

s= significant
Result was expressed as Mean± SD

Statistical analysis by unpaired t-test was done as a test of not significance
p value was not significant (>0.5)

It was observed that the mean ± SD blood ammonia level was (50.7± 10.8) µmol/L in medium esophageal varices group (n = 25) and (61.7± 21.0) µmol/L in large esophageal varices group (n = 22). Here p value is 0.026, which is statistically significant.

Figure-1 shows the scatter diagram between blood ammonia concentration and grades of esophageal varices. Spearman's rank order correlation analysis shows moderate positive correlation between blood ammonia concentration and grades of esophageal varices (r= 0.452) and corresponding p value was 0.001 which is statistically significant.

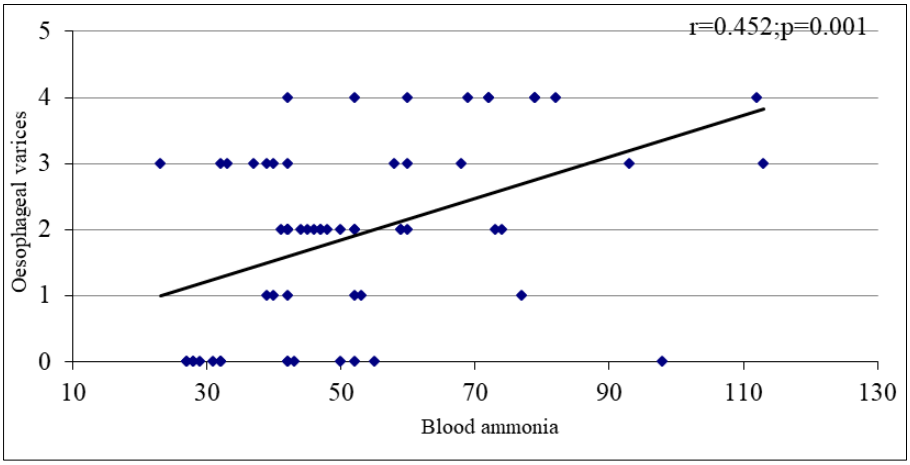

Figure 1: Spearman's rank correlation between blood ammonia and grades of esophageal varices.

Table-5: Receiver-operator characteristic (ROC) curve of blood ammonia for prediction of medium varices.

	Cut of value	Sensitivity	Specificity	Area under the ROC curve	95% Confidence interval (CI)	
					Lower bound	Upper bound
Blood ammonia (µmol/L)	39.5	96.0	56.2	0.765	0.597	0.933

The area under the receiver-operator characteristic (ROC) curves for prediction of medium varices is depicted in table-5. Based on the receiver-operator characteristic (ROC) curves blood ammonia had area under curve 0.765. Receiver-operator characteristic (ROC) was constructed by using blood ammonia, which gave a cut off value of 39.5 (umol/L), with 96.0% sensitivity and 56.2% specificity for prediction of medium varices.

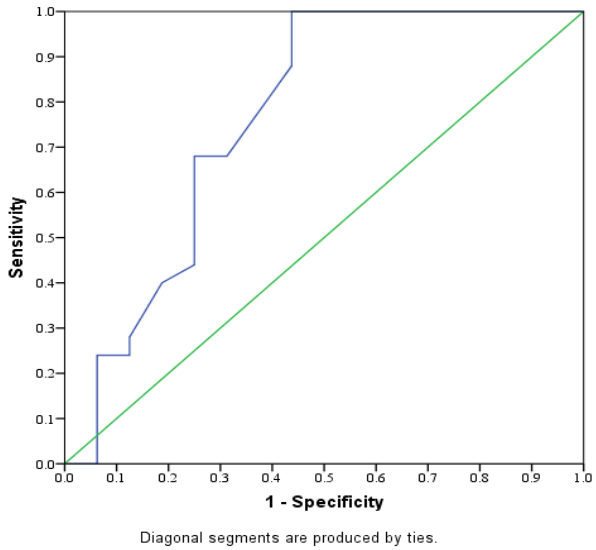

Figure 2: Receiver-operator characteristic (ROC) curve of blood ammonia for prediction of medium varices.

Table 6: Performance of blood ammonia as a diagnostic test for presence of medium varices (N=41)

Blood ammonia (µmol/L)	Medium varices		Total
	Present n = 25 (%)	Absent n = 16 (%)	
Positive >39.5	24 (96.0)	7 (43.7)	31 (75.6)
Negative ≤39.5	1 (4.0)	9 (56.3)	10 (24.4)
Total	25 (100.0)	16 (100.0)	41 (100.0)

Sensitivity: 96.0%
Specificity: 56.3%
Accuracy: 80.5%
Positive predictive value: 77.4%
Negative predictive value: 90.0%

Table-6 shows performance of blood ammonia levels as a diagnostic test for presence of medium varices. It was observed that 31 (75.6%) patients had positive blood ammonia level (>39.5 umol/L), among them 24 patients had medium varices and 7 patients had no medium varices. Ten (24.4%) patients had negative (≤39.5 umol/L) blood ammonia level, among them 1 patient had medium varices and 9 patients had no medium varices. Sensitivity of blood ammonia was found to be 96.0%, specificity 56.3%, positive predictive value 77.4%, negative predictive value 90.0% and accuracy 80.5%.

Table-7: Receiver-operator characteristic (ROC) curve of blood ammonia for prediction of large varices.

	Cut of value	Sensitivity	Specificity	Area under the ROC curve	95% Confidence interval (CI)	
					Lower bound	Upper bound
Blood ammonia (µmol/L))	56.5	59.1	93.7	0.778	0.624	0.933

The area under the receiver-operator characteristic (ROC) curves for prediction of large varices is depicted in table-7. Based on the receiver-operator characteristic (ROC) curves blood ammonia had area under curve 0.778. Receiver-operator characteristic (ROC) was constructed by using blood ammonia, which gave a cut off value of 56.5 (umol/L), with 59.1% sensitivity and 93.7% specificity for prediction of large varices.

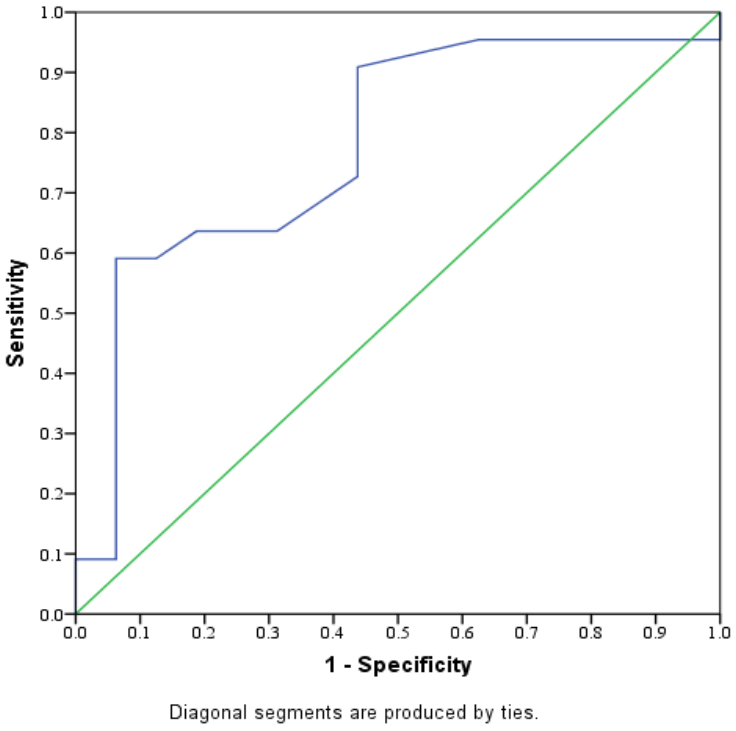

Figure 3: Receiver-operator characteristic (ROC) curve of blood ammonia for prediction of large varices.

Table 8: Performance of blood ammonia as a diagnostic test for presence of large varices (N=38)

Blood ammonia (umol/L)	Large varices		Total
	Present n= 22 (%)	Absent n= 16 (%)	
Positive >56.5	13 (59.1)	1 (6.9)	14 (36.8)
Negative ≤56.5	9 (40.9)	15 (93.8)	24 (63.2)
Total	22 (100.0)	16 (100.0)	38 (100.0)

Sensitivity: 59.1%
Specificity: 93.8%
Accuracy: 73.7%
Positive predictive value: 92.9%
Negative predictive value: 62.5%

Table-8 shows performance of blood ammonia levels as a diagnostic test for presence of large varices. It was observed that 14 (36.8%) patients had positive blood ammonia level (>56.5 umol/L), among them 13 patients had large varices and 1 patient had no large varices. Twenty four (63.2%) patients had negative (≤56.5 umol/L) blood ammonia level, among them 9 patients had large varices and 15 patients had no large varices. Sensitivity of blood ammonia was found to be 59.1%, specificity 93.8%, positive predictive value 92.9%, negative predictive value 62.5% and accuracy 73.7%.

DISCUSSION

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 by Hussain *et al.,* [9] 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.,* [3]. In his study 31 (56%) were male and 24 (44%) female. Hussain *et al.,* [9] 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.,* [10] 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.,* [11] where positive family history was in 21% cases. Fifteen (23.8%) patients had parental consanguinity and these were Wilson disease cases. Karim *et al.,* [11] found similarly parental consanguinity in 24% cases and all were Wilson disease. Rukunuzzaman *et al.,* [12] 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. 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.,[*13] Demirel *et al.,* [14] Alam *et al.,* [15] and Prabakaran *et al.,* [16] who found 87%, 91%, 86% and 93.5% cases of esophageal varices in their studies respectively. The mean blood ammonia concentration in medium and large esophageal varices was (50.7 ± 10.8) µmol/L and (61.7 ± 21.0) µmol/L respectively in current study which is similar with a study of Khondaker *et al.,* [8] That study showed mean blood ammonia concentration in medium and large esophageal varices were 72.0 ± 39.13 µmol/L and 97.75 ± 31.34 µmol/L respectively. In both study mean difference is statistically significant. Present study showed that the mean ammonia level was higher in esophageal varices group that was 56.2±17.9 µmol/L than non- esophageal varices group which was 40.5 ± 18.0 µmol/L, which is statistically significant (p value =0.004). Ramzy *et al.,* [7] found similar observation, but the result was not statistically significant. The mean blood ammonia concentration in grade I, II, III, IV esophageal varices was respectively 50.5 ± 14.3 µmol/L, 50.7 ± 9.9 µmol/L, 53.1 ± 26.9 µmol/L, 71.9 ± 19.0 µmol/L and here p value (0.002) is statistically significant. This progressive rise in blood ammonia for grade I, II, III and IV may be due to increase shunting of blood in more advanced varices. Ramzy *et al.,* [7] found different observation and the result was not statistically significant. A positive correlation between blood ammonia level and esophageal varices (r=0.452, p value = 0.001) was found in this study. Frequencies of esophageal varices increased as the blood ammonia level increased. Similar observation was made by some other researchers, eg. Khondaker *et al.,* [8] Tarantino *et al.,* [17] and Hassan *et al.,* [18] Study of Abo- Alsoud *et al.,* [19] showed a positive correlation between blood ammonia concentration and grading of esophageal varices (p= <0.001, r= 0.692), positive predictive value of 92.9%, negative predictive value of 62.5% and accuracy 73.7%. The analysis by the Receiver-Operating Characteristic curve using blood ammonia, which showed a cut off value of 39.5µmol/L, with 96.0% sensitivity and 56.2% specificity for prediction of medium varices and a cut off value of 56.5µmol/L, with 59.1% sensitivity and 93.7% specificity for

prediction of large varices. Current study shows, positive predictive value of 77.4%, negative predictive value of 90.0% and accuracy of 80.5% in medum esophageal varices. Positive predictive value 92.9%, negative predictive value 62.5% and accuracy 73.7% in large varices. Similar results were also observed in previous studies. Khondaker *et al.*, [8] found a cutoff point of blood ammonia concentration of 63 µmol/ L for detection of medium and /or large esophageal varices, where PPV was 65.5 %, NPV was 90.09 % and accuracy was 72.5% with a sensitivity of 95% and specificity of 50%. Similar observations were made by some other researchers [18, 19]. The cut off value varies among different studies among adult and children. The present study showed that, there is moderate positive correlation between blood ammonia concentration and grades of esophageal varices and blood ammonia concentration of ≥ 36.5 µmol/ L g/dl and ≥ 56.5 µmol/ L is an indicator of presence of medium and large esophageal varices in children with CLD respectively.

CONCLUSION

From this study it may be concluded that blood ammonia level positively correlates with the grades of esophageal varices in children with chronic liver disease. The present study showed that, there is moderate positive correlation between blood ammonia concentration and grades of esophageal varices and blood ammonia concentration of ≥ 36.5 µmol/ L g/dl and ≥ 56.5 µmol/ L is an indicator of presence of medium and large 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.

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