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ORIGINAL ARTICLE

HIGH BLOOD AMMONIA LEVEL IS A PREDICTOR OF MEDIUM AND LARGE SIZE ESOPHAGEAL VARICES IN CIRRHOTIC PATIENTS

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Abstract:

Background: *The development of esophageal varices (EV) and rupture of them are the most serious complications of portal hypertension. Upper gastrointestinal endoscopy is the gold standard for diagnosis of EV but it is a costly and troublesome invasive procedure. To find a non-invasive method for detection of size of EV and to predict the bleeding risk is appealing and would decrease the indications cost and discomfort of upper GI endoscopy. The aim of the study is to evaluate high blood ammonia level is a predictor of medium and large size of esophageal varices in Cirrhotic patients.* ***Methods:*** *This was an observational Cross-sectional study conducted on 40 cirrhotic patients in Department of Gastroenterology, BSMMU using a pre-designed data collection sheet. Information about clinical profile, laboratory parameters- blood ammonia, serum bilirubin, serum albumin, prothrombin time, and ultrasonography of abdomen, endoscopy upper GIT was collected and recorded. The collected data was analyzed by computer with the help of SPSS version 22. Statistical analysis was done by using appropriate statistical tool like Chi-square test, Student's t- test. P value < 0.05 was considered as significant. Diagnostic efficacy of blood ammonia was calculated by using a value.* ***Results:*** *A total of 40 patients with cirrhosis. Mean age of cirrhotic patients were 47.47±12.98 years. Mean blood ammonia of small size EV of cirrhotic patients was 73.70±32.11 (µmol/L) and medium and large size EV was 118.3±38.37 (µmol/L) (P< .001). At the level of 78.5 (µmol/L), sensitivity and specificity of blood ammonia was 95% and 65% respectively in detection of size of EV.* ***Conclusion:*** *Blood ammonia estimation could be a good tool for identifying individuals with medium and large size esophageal who will need to undergo endoscopy more frequently.*

Key words: *Blood ammonia, esophageal varices, Cirrhosis of liver.*

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Introduction:

Cirrhosis is a result of advanced liver disease, characterized by replacement of the liver tissue with fibrous tissue and regenerative nodules leading to loss of liver function[1]. Portal hypertension resulting from chronic liver disease is associated with the development of portosystemic collaterals, of which varices are of the greatest clinical significance due to their severe complications[2]. Approximately 5%-15% of patients with cirrhosis develop esophageal varices (EV) yearly, and most of them will develop gastrointestinal varices over their lifetime[3].

An increased portal pressure leads to an increased varix size and decreased varix wall thickness, thus leading to an increased variceal wall tension. The most important predictor of hemorrhage is the size of varices, with the highest risk of first hemorrhage occurring in patients with large varices, about 15% per year[4]. Being able to predict the presence of EV in patients with cirrhosis by a non-invasive method would decrease the necessity of endoscopic screening and reduce health care costs[2].

Several studies have evaluated possible noninvasive markers of esophageal varices in patients with

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cirrhosis, such as the platelet count, spleen size, portal vein diameter and transient elastography [5,6].

The raised blood ammonia level could be a good mirror of portosystemic collaterals as well as portal hypertension. Ammonia is a substance produced by intestinal bacteria and cells during the protein digestion. It is passed from the intestines to the liver through the portal vein. In the liver, ammonia is converted to glutamine, which is then metabolized into urea by the kidneys to be excreted. In a diseased liver, the ammonia is not broken down, and it accumulates in the blood. The major portion of ammonia carried by portal blood is shunted by portosystemic collaterals into systemic circulation[6].

Blood ammonia levels have been found to correlate well with the severity of liver disease and existence of portosystemic shunts, especially esophageal varices[7]. Accumulation of ammonia in splanchnic vessels in cases of liver function impairment results in vasodilatation and increased portal blood flow generating portal hypertension[8,9].

A recent study had found that the best blood ammonia value for the detection of EV was 123 ìg/dL and this value had a sensitivity of 70% and a specificity of 92%[10]. Another report from Bangladesh has revealed that a cutoff value of 77.5 umol/L (108.5 ìg/dL) ammonia with 100% sensitivity and 95% specificity for the detection of EV[11].

Upper GI endoscopy is the gold standard test to detect oesophageal varices. But screening all cirrhotic patients with upper GI endoscopy at a particular time interval to detect the presence of varices or transformation of small varices to medium and large varies implies a number of endoscopies, which increases the costs, patients discomfort and work load of endoscopy unit. Besides, it is difficult to perform repeated screening endoscopy in patients with some comorbid conditions like severe respiratory distress, cardiac arrhythmia, atlantoaxial subluxation etc.

Blood ammonia level is a valuable, cheaper, simple non-invasive test and is available in our country. Establishing such correlation would lead cirrhotic patients with high ammonia level to a suspicion of presence of varices.

So, this study was intended to find out the correlation of blood ammonia level with esophageal varices in patients with cirrhosis of different etiologies in Bangladeshi population. Establishing such correlation would lead cirrhotic patient with high ammonia level to a suspicion of having oesophageal varices, particularly medium or large varices. This will pinpoint patients who will require closer follow-up and endoscopic screening and who will require follow-up and endoscopic screening less frequently. The aim of the research is to evaluate the high blood ammonia level as a predictor of medium and large size oesophageal varices in Cirrhotic patients.

Methods:

It was a cross-sectional observational study conducted in the department of Gastroenterology, Bangabandhu Sheikh Mujib Medical University (BSMMU) from May 2019 to January2021. Study population was Cirrhotic patients attending the Department Gastroenterology, BSMMU. Purposive sampling technique was used. Forty patients with cirrhosis of liver with different size of esophageal varices (EV) were enrolled as study subject. Size of EV was divided into two groups, Group-A was small size EV and Group-B was medium and large size EV. Inclusion criteria of the patients were history and clinical features suggestive of cirrhosis of liver, ultrasonographic evidence of coarse liver echotexture and endoscopic evidence of oesophageal varices. Exclusion criterias were hepatic encephalopathy or coma. Because, patient is non cooperative and also blood ammonia high in this condition and hamper actual level , active GI bleeding and history of bleeding within two weeks,as blood ammonia become high in this condition and not represent the actual level, hepatocellular carcinoma, portal vein thrombosis,as blood ammonia becomes high in this condition whichinterfere actual blood ammonia level,previous intervention for varices, sclerotherapy, EBL as this patient usually is on another drugs like lactulose, beta blocker which interfere actual blood ammonia level, renal insufficiency evidenced by serum creatinine above upper limit of normal and whom endoscopy is contraindicated.

Endoscopic grading of esophageal varices is subjective. Various criteria have been used to try to standardize the reporting of oesophageal varices. The best known of these criteria are those compiled by the Japanese Research Society for portal Hypertension[12]. The descriptors include form (size) of the varix, red colour signs, colour of the varix, and location of the varix.

Patients who fulfill the inclusion criteria were taken for the study. A written consent was initially obtained from patients prior to enroll into the study. Total 40 cirrhotic patients of either sex and age between 18 to 70 years were the study sample. Detailed history was taken and clinical examination was carried out for each patient.

The endoscopy of the upper GIT was done by Olympus Video Endoscope at the endoscopy room in the presence and under direct supervision of the supervisor.

Varices were classified by the widely used semi - quantitative morphological assessment into small, medium and large varices.

The blood ammonia level of all the enrolled subjects was measured within 1-3 days of performing endoscopy. The sample was immediately carried to the laboratory gently in an ice box and analyzed within 30 minutes of arrival. All the blood ammonia level test was done in a single center to avoid the lab-to-lab report variation. After collection of all data, statistical analysis was performed.

After collection of data, all data were checked and cleaned. Data were analyzed by using statistical software SPSS 22. Quantitative data were expressed as mean and standard deviation, whereas qualitative data were count with percentage. Qualitative data were analyzed by Chi-square test and quantitative data by unpaired t- test. Performance of the test was assessed by sensitivity and specificity. ROC curve was used to assess the usefulness of the test and performance at different cutoff values. P value of less than 0.05 was considered statistically significant.

Results:

Out of 40 patients enrolled in this study, male was 29 (72.5%) and female was 11 (27.5%), male female ratio was 2.6:1. Most of the cirrhotic patients belongs to 35 to 44 years of age (Table -I).

Table-I

Distribution of the subjects according to age (n=40).

Age (years)	Cirrhotic patients n (%)
<25	2 (5.0)
25 - 34	5 (12.5)
35 - 44	13 (32.5)
45 - 54	8 (20.0)
≥55	12 (30.0)
Mean ± SD	47.47 ± 12.98

Regarding etiology of cirrhosis of liver, most of the cirrhosis of liver(77.5%) of the study were related to HBV while only 15 % were due to HCV infection and 7.5% due to other causes (Figure-1).

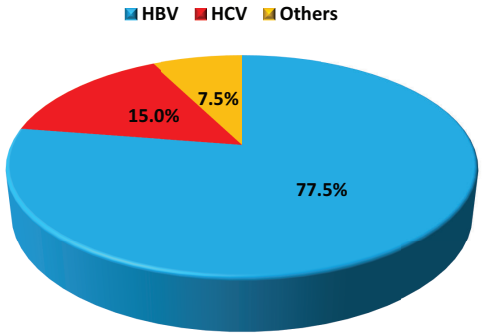

Figure-1: *Underlying cause of cirrhosis of liver of the study subject (n=40)*

Mean blood ammonia level was 73.7 (µmol/L)among patient having small varices and 118.3 (µmol/L) among patient having medium to large varices and it was statistically significant (Table-II).

Correlation of blood ammonia with different size of esophageal varices was studied and found a positive corelation (Figure 2).

Receiver-operator characteristic (ROC) curve was constructed by using blood ammonia level to medium to large oesophageal varices. The area under the receiver-operator characteristic (ROC) curves was 0.873.

Table-II

Difference in blood ammoniaamong patients of liver cirrhosis(n=40).

	Group -A(n=20) (Small size EV)	Group-B(n=20) (Medium and large size EV)	p-value
Blood ammonia(µmol/L)	73.70 ± 32.11	118.30± 38.37	<0.001*

Unpaired t- test was done to measure the level of significance, Significance at $p < 0.05$
*Significant

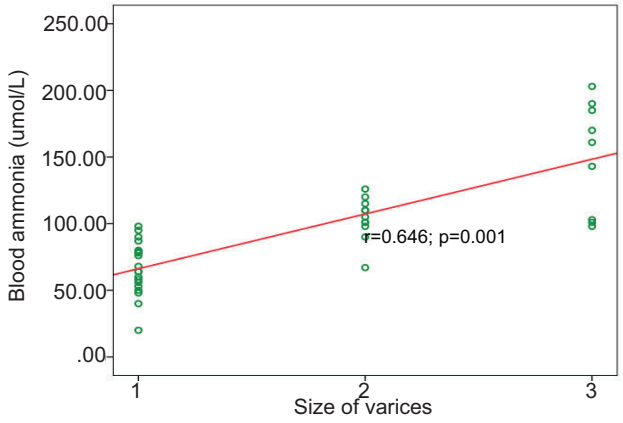

Figure 2: *Scatter plot diagram showingpositive significant spearman's rank correlation (r=0.646; p=0.001) between blood ammonia with different size of varices.*

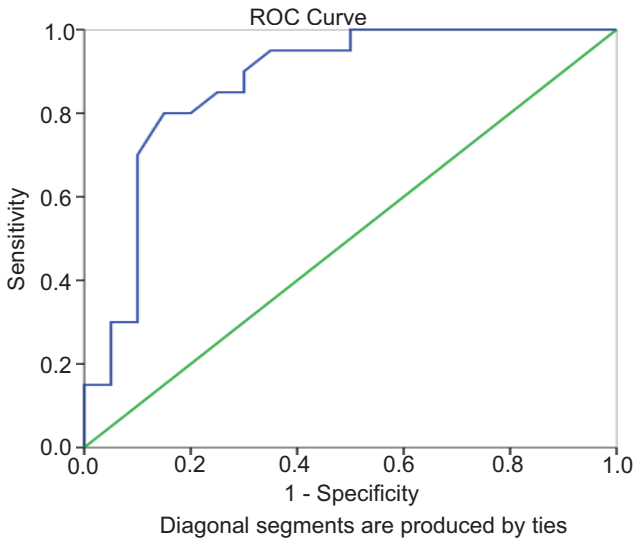

Figure 3: *The ROC curve was generated by plotting the true positive rate (sensitivity) against the false positive rate (1- specificity). Area under ROC curve showing 0.873 with 95% CI (0.757-0.988).The best cut off value of blood ammonia was determined at the highest point of Youden index, which was found 78.5 (µmol/L).*

Table-III

Performance of blood ammonia level at cut off value of 78.5 (µmol/L) for diagnosis of medium to large varices.

Blood ammonia(µmol/L)	Varices		Total	p-value
	Group- B, n (%) (medium &large size)	Group -A, n (%) (small size)		
e"78.5	19 (95.0)	7 (35.0)	26 (65.0)	
<78.5	1 (5.0)	13 (65.0)	14 (35.0)	<0.001*
Total	20 (100.0)	20 (100.0)	40(100.0)	

Chi-Square test was done to measure the level of significance, Significance at p <0.05, *Significant

	%	95% CI	
		Min	Max
Sensitivity	95.0	78.6	99.7
Specificity	65.0	48.6	69.7
PPV	73.1	60.5	76.7
NPV	92.9	69.4	99.6
Accuracy	80.0	63.6	84.7

Discussion:

In this study, a total 40 cirrhotic patient were enrolled. The mean age of the participant was 47.47 ± 12.98 years. In another study by Ullah P et al., (2023)at Dhaka Medical College Hospitalin Bangladesh, reported the mean age 47.00±14.53 years which is consistent with our study.[13]In this study, male was 29(72.5%) and female was 11(27.5%), male female ratio was 2.6:1. This gender distribution is also consistent with the finding ofUllah P et al, where they also found male 57(71%) and female 23(29%), with male to female ratio 2.4:1.[13] Regarding etiology, 77.5% of the cirrhosis of liver was related to HBV while only 15 % were due to HCV and rest 7.5% due to other causes.Mamun-Al-Mahtab et al., (2015) reported that,HBV is the leading cause of CLD in our country. They found HBV is related to 61.15% cases of cirrhosis of liver and HCV wasresponsible for 4.1% in Sylhet and 5% in Barisal divisions, respectively.[14]Ullah P et al., (2023) reported that 40(50%) patients had HBV followed by10(12.5%) had HCV and 30(37.5%) in others etiology of cirrhosis.[13]So, our etiology of cirrhosis is consistent with the previous report from Bangladesh.

The reference value of normal venous plasma ammonia level is (11-32 μmol/L)). The cirrhotic patients were grouped into small size EV and medium, large size EV.The mean ammonia concentration in small size EV was (73.70 ± 32.11) and in medium and large size EV was (118.30 ± 38.37). The mean difference was significant at P value < 0.001.

Blood ammonia, the newly suggested non-invasive marker of oesophageal varices showed significant difference in between small size EV and medium, large size EV groups (P= <0.001) in the present study. Also in spearman's rho correlation test, blood ammonia level showed positive correlation with the size of oesophageal varices (rho 0.646, P = 0.001). Degree of correlation found in the present study was comparable with that reported by Tarantino et al.,[7](2009) where rho was 0.43 and P value was < 0.001 and Khandaker et al.,[11](2013) where rho was 0.451 and P value was (< 0.001).

To test the blood ammonia level as a predictor of medium and large EV varices, sensitivity and specificity of blood ammonia level at different cutoff values were assessed. Blood ammonia at 78.5 (μmol/L) had sensitivity of 95 % and specificity of 65 % in detecting medium and large size esophageal varices in patients with cirrhosis. Its PPVwas 73.1 %and NPV was 92.9 % with accuracy of 80 %.Study done by Khandaker et al., 2013 where Blood ammonia at 63 (μmol/L) had sensitivity of 95 % and specificity of 50 % in detecting medium and large size esophageal varices in patients with cirrhosis. Its PPVwas 65.5 % and NPV was90.9 % with accuracy of 72.5 %.[11]

If cut of value was raised further, sensitivity decline and specificity increased. In relation to detection of medium and large varices by means of a non-invasive marker, sensitivity is more important than specificity. So cut off value 78.5 (μmol/L) was found better than other values in predicting medium and large size EV.

A study done byEl-Hefny et al., (2013), reported a cutoff value of 77.5 (μmol/L), ammonia with 100% sensitivityand 95% specificity for the detection of EV.[15] In the present study, the cut off value of blood ammonia 78.5 (μmol/L) set for detecting medium and large size EV treatment requiring large varices was comparable with the above result.

Another study upon 153 consecutive patients with Liver cirrhosis of various etiology have shown that blood ammonia level correlates well with the severity of liver disease as well as with the presence of different portosystemic shunts, particularly esophageal varices of different grades. The sensitivity and specificity of ammonia in predicting esophageal varices presence was 97% and 43% respectively with the cutoff value of ammonia 42 (μmol/L).[9]

According to the results of the present study, patients with high levels of ammonia should undergo endoscopy faster and those with lower levels may undergo less frequently. This study shows that blood ammonia is a good predictor for detection of medium and large size esophageal varices in cirrhotic patients which may be a useful marker for assessment necessity of endoscopy for these patients.

Conclusion:

So, blood ammonia could be a good tool at identifying individuals with medium and large esophageal varices who will need to undergo endoscopy more frequently.

Limitations:

Small sample size and this single hospital based study did not reflect exact scenario of the whole community.

Data Availability:

The datasets analysed during the current study are not publicly available due to the continuation of analyses but are available from the corresponding author on reasonable request.

Conflict of Interest:

The authors stated that there is no conflict of interest in this study

Funding:

This research received no external funding.

Ethical consideration:

The study was conducted after approval from the Institutional Review Board of Bangabandhu Sheikh Mujib Medical University. The confidentiality and anonymity of the study participants were maintained.

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