

Right liver lobe diameter to serum albumin ratio and blood ammonia level as non-invasive predictor for the presence of esophageal varices and the risk of bleeding in patient of cirrhosis of liver

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Abstract

Background: Esophageal varices (EV), a dangerous complication of cirrhosis, are expensive and inconvenient to diagnose with frequent endoscopies. This study explores using blood tests (ammonia level) and a liver size measurement (right lobe diameter to albumin ratio) as simpler ways to identify patients with EV and at risk of bleeding.

Materials and Methods: A cross-sectional study was conducted at BIRDEM General Hospital from April 2019 to June 2021 to investigate non-invasive predictors of esophageal varices in patients with liver cirrhosis. 153 patients with cirrhosis were enrolled and underwent detailed medical history, physical examination, and laboratory tests. Data was collected using standardized forms, checked for accuracy, and analyzed using SPSS 23 software.

Results: The study found that patients with esophageal varices (EV) had significantly higher blood ammonia levels ($41.13 \mu\text{mol/l} \pm 11.22$) compared to those without EV ($p < .05$). Additionally, the right liver lobe diameter was larger in patients with EV ($153.92 \text{ mm} \pm 6.54$) and the ratio of this diameter to their serum albumin level was also significantly higher (3.89 ± 0.91 , $p < .05$). Interestingly, a ratio of right liver lobe diameter to serum albumin greater than or equal to 2.95 identified patients with EV with 100% sensitivity and 86.4% specificity, offering a high degree of accuracy (86.4%). Blood ammonia levels above $33.35 \mu\text{mol/l}$ showed slightly lower accuracy (78.4%) with 79.4% sensitivity and 72.7% specificity. The study also followed the patients for bleeding complications. Nearly 38.4% experienced bleeding within 3 months, and a significant portion (65%) had both high right liver lobe diameter to albumin ratio and elevated blood ammonia levels at the 6-month mark.

Conclusion: This study found that the higher value of both the Right Liver Lobe Diameter to Serum Albumin Ratio and Blood Ammonia Level were significantly associated with the presence of esophageal varices (EV) among patients with liver cirrhosis and both of them can be used as non-invasive predictor of EV among patients with liver cirrhosis. However, further study is recommended to validate these findings.

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Keywords: Blood Ammonia; Esophageal Varices (EV); Right Liver Lobe Diameter (RLLD); Serum Albumin.

1. Introduction

Esophageal varices (EV) are a serious complication of cirrhosis, a chronic liver disease characterized by degeneration of liver cells, fibrosis, and abnormal regenerative nodules. Portal hypertension, a condition of high blood pressure in the portal vein of the liver, is a major consequence of cirrhosis and is directly linked to the formation of EV [1]. EV develop when portal hypertension causes blood to divert from the liver through alternative pathways called Porto systemic collaterals. These enlarged vessels, most commonly found at the gastro esophageal junction, are susceptible to bleeding, which can be life-threatening [2, 3]. Early detection of EV is crucial for preventing bleeding. Endoscopy is the gold standard for EV diagnosis, but it is an invasive procedure with limitations. In resource-limited settings like Bangladesh, where chronic hepatitis B prevalence is high, widespread endoscopic screening is impractical [4, 5]. 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. So, ammonia concentrations can be high in portal venous blood. In the liver, ammonia is converted to glutamine, which is then metabolized into urea by the kidneys to be excreted. The reference range for ammonia is 11-35 $\mu\text{mol/L}$ [6, 7]. In a diseased liver, the ammonia is not broken down and it accumulates in the blood. So, its level correlates well with the severity of EV and shares a relationship with it [8]. Albumin is quantitatively the most important plasma protein synthesized by the liver. The average size of the albumin pool in adults is 500 gm. Between 12 and 15 g is synthesized daily by the normal liver. Cirrhotic patients can only synthesize about 4 g (35 mg/kg per day in Child C cirrhosis) [9]. The fractional synthetic rate of albumin is approximately 6% per day compared with 25% for total liver protein. In liver disease, the fall in serum albumin concentration is slow as the half – life of albumin is about 22 days. Thus, a patient with acute hepatitis may have a virtually normal serum albumin value while lower levels would be expected in decompensated cirrhotic patients [10, 11]. The RLLD to Serum Albumin ratio in cirrhotic liver patients increases compared to control as serum albumin level is decreased [12]. At a cut-off point of 3.7-4.2, the sensitivity, specificity, and accuracy to predict EV were 95, 76.4, and 90% [13, 14]. Given the high prevalence of cirrhosis of liver disease in our context and limitations of the endoscopy is essential to find the adequate non-invasive predictors of the EV. This study aims to identify non-invasive predictors of EV in patients with cirrhosis. We investigate the potential of the right liver lobe diameter (RLLD) to serum albumin ratio and serum ammonia levels as markers for EV presence and bleeding risk.

2. Study Design and Methods

This was a cross-sectional study with a prospective observational component, conducted at BIRDEM General Hospital in Dhaka, Bangladesh, between April 2019 and June 2021. The study included patients with cirrhosis of the liver admitted to both inpatient and outpatient departments of the hospital's Gastrointestinal Hepatobiliary and Pancreatic Disorders (GHPD) unit.

2.1. Inclusion criteria

- Diagnosed with cirrhosis of the liver (new or previous)
- Diagnosed based on clinical, laboratory, radiological, and endoscopic findings

2.2. Exclusion criteria

- Pregnant women
- Liver with space-occupying lesions (SOL)
- Intra-abdominal tuberculosis or malignancy
- Active gastrointestinal (GI) bleeding or history within 2 weeks
- Recent beta-blocker use or endoscopic treatment for esophageal varices (within 4 weeks)
- Endoscopy contraindicated
- Hepatic encephalopathy or portal vein thrombosis
- End-stage renal disease (ESRD) or heart failure

2.3. Sampling

A purposive sampling technique was used to enroll patients meeting the inclusion criteria, regardless of the cause of cirrhosis.

2.4. Data Collection

- **Clinical Evaluation:** A detailed history and physical examination were performed for each participant.
- **Questionnaire:** A researcher-administered questionnaire collected information on:
 - Chronic liver disease history
 - Alcohol intake
 - Hepatic encephalopathy
 - Hematemesis (vomiting blood)
 - Melena (black stools)
 - Ascites (fluid buildup in the abdomen)
 - Edema (swelling)
 - Medication history
 - Previous endoscopic therapy
 - Other co-morbidities
- **Laboratory Tests:**
 - Complete blood count (CBC)
 - Liver function tests (LFTs)
 - Renal function tests (RFTs)
 - Fasting blood ammonia
- **Imaging:** Abdominal ultrasonography (USG) to measure the right lobe liver diameter (RLLD)
- **Endoscopy:** Upper GI endoscopy was performed by a single experienced endoscopist to assess the presence and grade of esophageal varices. Variceal size was categorized as small (grade I), medium (grade II), or large (grade III).
- **Blood Ammonia Measurement:** Fasting blood ammonia levels were measured within 1-3 days of endoscopy. Strict protocols ensured proper sample collection, storage, and analysis within 30 minutes.
- **Data Analysis:** Collected data were checked for errors and analyzed using SPSS-23 software. Statistical tests included independent samples t-tests and one-way ANOVA for comparisons. Results were presented as means, standard deviations (SD), and percentages. A receiver operating characteristic (ROC) curve analysis was performed to determine the best cut-off value for the RLLD/Serum Albumin ratio for optimal sensitivity, specificity, and accuracy. Statistical significance was set at $p \leq 0.05$ with a 95% confidence interval.

3. Results

This was a cross sectional study conducted in department of Gastrointestinal, Hepatobiliary and Pancreatic Disorders (GHPD), BIRDEM General Hospital, Dhaka, Bangladesh. A total of 200 subjects were enrolled in the study, with 153 completing it. Table shows that 48.4% of respondents were aged between 41 to 60 years, and 41.8% of respondents had above 60 years, beside only 9.8% were aged between 21 to 40 years. Mean age of the patients was 56.95 ± 11.9 years of SD. 69.3% were male and 30.7% were female. Table II shows 66% had DM, 51.6% had HTN, 16.3% had IHD, 19.6% had family history of liver disease, 5.9% had history of Alcohol consumption, 88.9% had anemia, 64.7% had Oedema, 36.6% had Jaundice and 20.3% had Leukonychia. Table III shows that mean, S. Bilirubin was 3.29 ± 5.77 mg/dl, S. Albumin was 29.05 ± 8.06 g/dl, AST was 71.85 ± 69.06 IU/L, ALT was 55.05 ± 79.46 IU/L, ALP was 139.64 ± 84.43 IU/L, HB% was 10.13 ± 2.54 gm/dl, Platelet was 170423.51 ± 241359.689 mm³, WBC was 7288.34 ± 3848.199 mm³, S. Creatinine was 1.25 ± 0.82 mg/dl, PT was 15.31 ± 5.76 sec, Blood Ammonia was 41.13 ± 11.22 μmol/l, Right liver lobe diameter was 153.92 ± 6.54 mm and Right liver lobe diameter and Serum albumin ratio was 3.89 ± 0.91 . Bar chart shows that according to Child-Turcotte-Pugh Grade, 15.7% had Grade A, 55.6% had Grade B and 28.8% had Grade C. Table IV shows that 85.6% respondents had esophageal varices. Table V shows that 24.8% had Grade I, 39.9% had Grade II, and 20.9% had Grade III of esophageal varices. Table VI shows that Blood Ammonia and Right liver lobe diameter to Serum albumin ratio was significantly higher in Liver cirrhosis with EV than without EV. Table VII shows that Right liver lobe diameter to Serum Albumin Ratio was significantly increased with the grade of EV ($p < 0.01$). Table VIII the cut-off value for right liver lobe diameter to serum albumin ratio was 2.95. Sensitivity 100%, Specificity 86.4%, PPV 97.8%, NPV 100% & Accuracy 98%. Table-IX shows Among 131 cases of EV a cut-off value of Right liver lobe diameter to Serum albumin ratio ≥ 2.95 could detect truly 131 cases. Among 22 cases with no EV a cut-off value of Right liver lobe diameter to Serum albumin ratio < 2.95 could detect truly 19 cases. Table X shows that Blood ammonia level significantly increased with the grade of EV. Table XI shows the cut-off value for blood ammonia level was 33.35. Sensitivity 79.4%, Specificity 72.7%, PPV 94.4%, NPV 37.2% & Accuracy 78%. Table XII shows Among 131 cases of EV a cut-off value of Blood Ammonia ≥ 33.35 μmol/l could detect truly 104 cases and among 22 no EV patient's Blood Ammonia < 33.35 could truly detect 16 patients. A binary logistic regression was conducted to figure out the association of risk of bleeding at 3 month with the RLLD to Serum Albumin ratio and Blood Ammonia level. No significant association was found in the analysis. However, the odds for bleeding due to blood ammonia was 1.019

(0.984 – 1.055). A binary logistic regression was conducted to figure out the association of risk of bleeding at 6 month with the RLLD to Serum Albumin ratio and Blood Ammonia level. No significant association was found in the analysis.

Table 1 Demographic characteristics of the study population (n=153)

Age group	Frequency (n)	Percentage (%)
21 to 40 years	15	9.8
41 to 60 years	74	48.4
Above 60 years	64	41.8
Mean ± SD		56.95 ± 11.9
Gender		
Male		69.3
Female		30.7

Data expressed with frequency, percentage and mean±SD.

Table 2 Clinical characteristics of the study population (n=153)

Clinical Parameter	Frequency (n)	Percentage (%)
DM	101	66.0
HTN	79	51.6
IHD	25	16.3
Family history of liver disease	30	19.6
History of Alcohol consumption	9	5.9
Anemia	136	88.9
Oedema	99	64.7
Jaundice	56	36.6
Leukonychia	21	20.3

*Multiple answers considered Here, DM= Diabetes Mellitus, HTN= Hypertension, IHD= Ischemic Heart Disease,

Table 3 Laboratory investigations of the respondents (n=153)

Investigations	mean±SD
S. Bilirubin (mg/dl)	3.29 ± 5.77
S. Albumin (g/dl)	29.05 ± 8.06
AST (IU/L)	71.85 ± 69.06
ALT (IU/L)	55.05 ± 79.46
ALP (IU/L)	139.64 ± 84.43
Hb% (gm/dl)	10.13 ± 2.54
Platelet (/mm ³)	170423.51 ± 241359.689
WBC (/mm ³)	7288.34 ± 3848.199

S. Creatinine (mg/dl)	1.25 ± 0.82
PT (sec)	15.31 ± 5.76
Blood Ammonia (µmol/l)	41.13 ± 11.22
Right liver lobe diameter (mm)	153.92 ± 6.54
Right liver lobe diameter/ Serum albumin	3.89 ± 0.91

Data expressed with mean±SD. AST= Aspartate aminotransferase, ALT= Alanine aminotransferase, ALP= Alkaline Phosphatase, PT= Prothrombin Time.

3.1. Esophageal varices among respondents

Table 4 Distribution of the respondents by esophageal varices (n=153)

Esophageal varices	Frequency (n)	Percentage (%)
Present	131	85.6
Absent	22	14.4
Total	153	100

Data expressed with frequency and percentage.

3.2. Grading of esophageal varices as per presence and size

Table 5 Distribution of the respondents by presence and size of varices (n=153)

Esophageal varices	Frequency (n)	Percentage (%)
No varices	22	14.4
Grade I	38	24.8
Grade II	61	39.9
Grade III	32	20.9
Total	153	100

Data expressed with frequency and percentage.

3.3. Blood ammonia and right liver lobe diameter to serum albumin ratio of the respondents

Table 6 Distribution of the respondents by blood ammonia and right liver lobe diameter to serum albumin ratio (n=153)

	Liver cirrhosis with EV (n=131)	Liver cirrhosis without EV (n=22)	P value
	mean±SD	mean±SD	
Blood Ammonia	42.24±11.35	36.34±9.13	*0.022
Right liver lobe diameter/ Serum albumin	4.12±0.72	2.55±0.83	*0.01

*P value was determined by independent sample t test. Data expressed with mean±SD.

3.4. Association of different grade of EV with right liver lobe diameter to serum albumin ratio

Table 7 Association of different grade of EV with right liver lobe diameter to serum albumin ratio (n=153)

Grade of EV	Right liver lobe diameter to Serum Albumin Ratio	P value
	mean±SD	
No varices	2.55±0.76	*<0.01
Grade I	3.29±0.33	
Grade II	4.12±0.09	
Grade III	5.11±0.42	

*P value was determined by One-way ANOVA test. Data expressed with mean±SD.

Table 8 Youden Index: (right liver lobe diameter to serum albumin ratio)

Cut-off	Sensitivity	Specificity	PPV	NPV	Accuracy	youden index (j=sen+spe-1)
2.85	1	0.682	0.949	1.000	0.954	0.682
2.95	1	0.864	0.978	1.000	0.980	0.864
3.03	0.954	0.864	0.947	0.714	0.915	0.818

Table 9 Cross tabulation of EV with Right liver lobe diameter to Serum albumin Ratio based on derived cut-off value

RLLD to Serum albumin Ratio	Liver Cirrhosis with EV	Liver Cirrhosis without EV	Total
≥2.95	True Positive 131	False Positive 3	All patient (TP+FP) 134
<2.95	False Negative 0	True Negative 19	All patient (FN+TN) 19
	All patients with EV (TP+FN) 131	All patients without EV (FP+TN) 22	153

EV= Esophageal Varices

Table 10 Association of different grade of EV with blood ammonia level (n=153)

Grade of EV	Serum Ammonia(μmol/l)	P value
	mean±SD	
No varices	36.35±9.13	
Grade I	38.57±8.10	
Grade II	43.73±12.57	
Grade III	43.77±11.52	*0.01

*P value was determined by One-way ANOVA test. Data expressed with mean±SD.

3.5. Cut-off value

Table 11 Youden Index: (Blood ammonia)

Cut-off	Sensitivity	Specificity	PPV	NPV	Accuracy	youden index (j=sen+spe-1)
33.15	0.794	0.682	0.937	0.357	0.778	0.476
33.35	0.794	0.727	0.945	0.372	0.784	0.521
33.75	0.779	0.727	0.944	0.356	0.771	0.506

Table 12 Cross tabulation of EV with blood ammonia based on derived cut-off value

Blood Ammonia	Liver Cirrhosis with EV	Liver Cirrhosis without EV	Total
≥33.35 μmol/l	True Positive 104	False Positive 6	All patient (TP+FP) 110
<33.35 μmol/l	False Negative 27	True Negative 16	All patient (FN+TN) 43
	All patients with EV (TP+FN) 131	All patients without EV (FP+TN) 22	153

EV= Esophageal Varices

3.6. Association of Blood ammonia and RLLD/Albumin with risk of bleeding at 3 month

Table 13 Association of Blood ammonia and RLLD/Albumin with risk of bleeding (n=125)

	OR	95% C.I.for EXP(B)		P value
		Lower	Upper	
Blood ammonia	1.019	0.984	1.055	0.303
RLLD/Albumin	0.951	0.628	1.440	0.812

3.7. Association of Blood ammonia and RLLD/Albumin with risk of bleeding at 6 month

Table 14 Association of Blood ammonia and RLLD/Albumin with risk of bleeding (n=120)

	OR	95% C.I.for EXP(B)		P value
		Lower	Upper	
Blood ammonia	0.973	0.934	1.013	0.187
RLLD/Albumin	0.868	0.558	1.351	0.530

3.8. Child-Turcotte-Pugh grading of the respondents

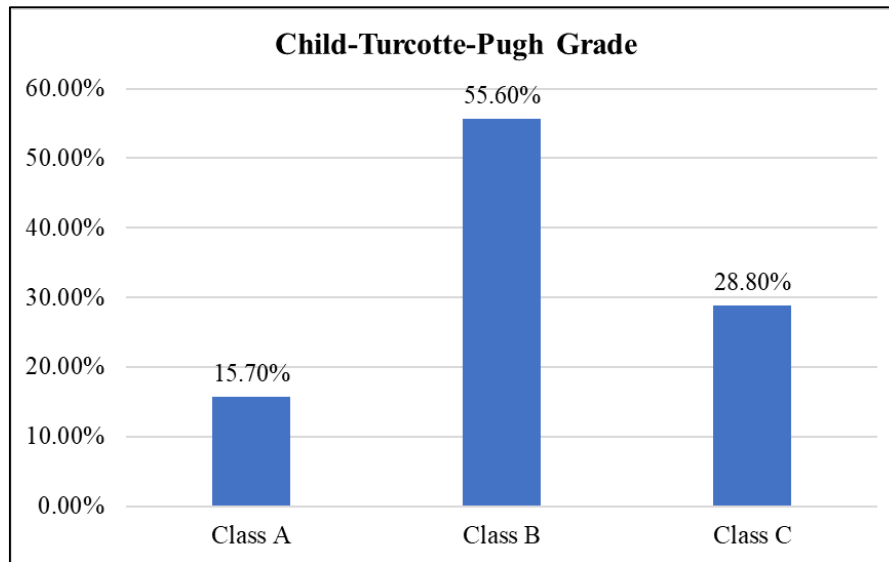


Figure 1 Distribution of the respondents by Child-Turcotte-Pugh grade (n=153)

4. Discussion

Sensitivity and specificity of numerous non-invasive parameters have been investigated for the assessment of presence and size of esophageal varices and risk prediction for bleeding. The aim of this study was to evaluate the use of ratio between the diameter of right liver lobe and serum albumin concentration and blood ammonia level as preliminary indirect parameter of the presence of portal hypertensive changes in upper gastrointestinal endoscopy. Total number of respondents was 153. In this study, the majority of respondents (48.4%) fell within the age range of 41 to 60 years. Conversely, only 9.8% were between 21 and 40 years old, while 41.8% were above 60 years old. The mean age of the patients was 56.95 years old with a standard deviation (SD) of 11.9 years. Previous studies reported similar findings: Sarkar et al. (2018) found a mean age of 53.8 years (SD = 13.7 years) among 65 patients with cirrhosis¹⁵. Akram et al. (2019) observed a mean age of 56.04 years (SD = 10.22 years)¹⁴. This study observed a male predominance, with 69.3% of respondents being male and 30.7% female. This aligns with findings from other studies: Akram et al. (2019) also reported a majority male population (60%)¹⁴. Sarkar et al. (2018) found males (66.2%) to be predominant in their study¹⁵. In this study 88.9% had anemia, 64.7% had edema, 36.6% had Jaundice, 20.3% had Leukonychia, 66% had DM, 51.6% had HTN, 16.3% had IHD and 5.9% had history of Alcohol consumption. Beside 19.6% had family history of liver disease. In the study of Sarkar et al. 52.3% had Oedema, 60% had Leukonychia, 43.1% Anemia and 9.2% had jaundice¹⁵. Among all the respondents mean S. Bilirubin was 3.29±5.77 mg/dl, S. Albumin was 29.05±8.06 g/dl, AST was 71.85±69.06 IU/L, ALT was 55.05±79.46 IU/L, ALP was 139.64±84.43 IU/L, HB% was 10.13±2.54 gm/dl, Platelet was 170423.51±241359.689 mm³, WBC was 7288.34±3848.199 mm³, S. Creatinine was 1.25±0.82 mg/dl, PT was 15.31±5.76sec, Blood Ammonia was 41.13±11.22 μmol/l, Right liver lobe diameter was 153.92±6.54 mm and Right liver lobe diameter and Serum albumin ratio was 3.89±0.91. In a previous study researcher observed Akram et al observed mean serum albumen level was 23.58 ± 3.72 g/dL and right liver lobe size/albumin concentration ratio were 4.20¹⁴. In another study by Alempijevic et al. mean value of right liver lobe diameter/ albumin ratio was 5.51 ± 1.82¹⁶. According to Child-Turcotte-Pugh Grade, 15.7% had Grade A, 55.6% had Grade B and 28.8% had Grade C. Beside Among all the patients 85.6% respondents had esophageal varices. According to Grades of esophageal varices 14.4% had no varices, 24.8% had Grade I, 39.9% had Grade II and 20.9% had Grade III. In a previous study by Akram et al. according to Child-Turcotte-Pugh Grade 67 had Grade A, 61 Grade B and 32 had Grade C also observed 76.5% had esophageal varices where 51 (31.88%) patients had esophageal varices grade II, followed by 39 (24.37%) patients with grad I esophageal varices, Grade III and grade IV esophageal varices were found in 24 (15.00%) and 8 (5.00%) patients, respectively and grade 0 or no varices in 38 (23.75%) patients¹⁴. In the study of Elzeftawy et al. among 359 patients 218 had EV and 141 had no EV⁸. According to this study Right liver lobe diameter to Serum albumin ratio was significantly higher in liver cirrhosis with EV than without EV and also right liver lobe diameter to Serum Albumin Ratio was significantly increases with the grade of EV (p<0.01). A cut-off value of Right liver lobe diameter to Serum albumin ratio ≥ 2.95 showed respectively 100%, 86.4%, 97.8%, 100% and 98.0% sensitivity, specificity, PPV, NPV and accuracy. Akram et al. revealed that the right liver lobe size/albumin concentration ratio, can help physicians to restrict the use of endoscopic screening only to patients presenting a high probability of esophageal varices and observed the

similar findings where sensitivity was 86.89%, specificity was 78.95%, positive predictive value was 92.98% and negative predictive value was 65.22% also observed a diagnostic accuracy of 85% in the study¹⁴. In the study of Alempijevic et al. statistically significant correlation was proved between EV grade and Right liver lobe diameter to Serum albumin ratio. Cut-off value of the right liver lobe/serum albumin concentration ratio for diagnosis of varices was 4.425 where the sensitivity was 83.1% and the specificity was 73.9%¹⁶. It was also observed that Blood Ammonia was significantly higher in liver cirrhosis with EV than without EV. Blood ammonia level significantly increases with the Grade of EV ($p < 0.05$). A cut-off value of Blood Ammonia ≥ 33.35 $\mu\text{mol/l}$ showed respectively 79.4%, 72.7%, 94.50%, 37.2% and 78.4% sensitivity, specificity, PPV, NPV and accuracy. Previous study by Elzeftawy et al. blood ammonia level may be clinically useful as it correlates with and is an independent predictor for both endoscopic risk signs and risk factors of bleeding and also observed blood ammonia level was significantly higher in patients with EV than in those without it ($p < 0.001$) and cut-off value for prediction of the presence of varices was >123 $\mu\text{g/dL}$, yielding a sensitivity and specificity of 70% and 92%, respectively and an accuracy of 83.4%⁸. In 20-40% of cirrhotic patients with EV, variceal bleeding occurs, and it has a significant morbidity and mortality (about 17-57% from each episode of variceal bleeding) (Garcia-Tsao et al¹⁷. In the present study, 38.4% patients experienced bleeding at 3 month and 65% at 6 month, which are in line with the study of Nouh et al¹⁸. However, no significant association was found for variceal bleeding with RLLD to Serum Albumin ratio and blood ammonia level.

5. Conclusion

The present study found that the higher value of both the right liver lobe diameter to serum albumin ratio and blood ammonia level were significantly associated with the presence of esophageal varices (EV) among patients with liver cirrhosis. In addition, the RLLD to Serum Albumin ratio and Blood Ammonia level showed higher sensitivity and specificity in detecting EV. Besides, risk of bleeding was higher than other studies, directing EV as a major concern to deal with for liver cirrhosis patients. However, further study is recommended countrywide to validate these findings.

Compliance with ethical standards

Acknowledgments

Acknowledges study population & department of cardiology.

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

An ethical clearance was taken from BIRDEM Academy.

Statement of informed consent

Informed consent was obtained, with participants having the freedom to withdraw at any point.

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