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Non-Invasive Parameters of Oesophageal Varices Diagnosis: Which Sensitive and Applicable; A Pilot Study

Elham Ahmed Hassan[1*], **Abeer Sharaf El-din Abd El-rehim**[1], **Zain El-Abdeen Ahmed Sayed**[2], **Emad Farah Mohamed Kholef**[3], **Mostafa Abdullah Mohammed Hareedy**[2] and **Refaat Fathy Abd EL-aal**[2]

[1]Department of Tropical Medicine and Gastroenterology, Faculty of Medicine, Assiut University, Egypt

[2]Department of Internal Medicine, Faculty of Medicine, Assiut University, Egypt

[3]Department of Clinical Pathology, Faculty of Medicine, Aswan University, Egypt

*Corresponding Author: Elham Ahmed Hassan, Assiut University Hospital, Tropical Medicine and Gastroenterology, 6th floor, Assiut, Egypt, Tel: +201002963415; Fax: +20882333327; E-mail: mam_elham75@yahoo.com

Abstract

Background: Oesophageal varices (OV) have the greatest clinical impact. Upper endoscopy is the gold standard for OV diagnosis, despite its own limitations. Non-invasive detection of OV promises to decrease the necessity of endoscopic screening.

Objectives: To assess blood ammonia level, spleen longitudinal (SLD), portal vein (PVD), splenic vein (SVD) diameters, platelets count and platelets/SLD ratio to evaluate their predictive accuracy as non-invasive indicators for the presence of OV and their correlation with variceal size.

Patients and methods: This was a prospective study. Sixty cirrhotic patients were screened using upper endoscopy (for the presence and size of OV) and abdominal ultrasonography (for measurement of PVD, SVD, SLD). Fasting blood ammonia level, platelets / SLD ratio were measured.

Results: Blood ammonia, PVD, SVD and SLD were significantly higher in patients with OV than those without (P < 0.001 for all). Using area under receiver operating characteristic curve (AUC), these parameters were good predictors for the presence of OV where, PVD had the highest AUC (I.00) followed by blood ammonia (AUC 0.99). Blood ammonia level correlated with variceal size (rho = 0.442, P = 0.002).

Conclusion: Blood ammonia, PVD, SVD and SLD were good non-invasive predictors for OV presence with the superiority of PVD and ammonia. Blood ammonia level could be clinically useful, as it correlated with the size of OV so, pinpoint those patients requiring closer follow-up and endoscopic screening.

Keywords: Oesophageal varices; Blood ammonia; Spleen longitudinal diameter; Portal vein diameter; Splenic vein diameter

Introduction

Oesophageal varices (OV), formed as a result of portal hypertension, have a great clinical impact due their severe complications [1]. While they are found in approximately 50% in cirrhosis, they are developed at a rate of 8% per year in patients without varices. The progression from small to large varices occurs in 10 to 20% of cases yearly and their presence correlates with the severity of liver disease [2]. Variceal hemorrhage develops at a yearly rate of 5 to 15%, where the most important predictor of hemorrhage occurring with large varices [3,4].

The American association for the study of liver disease single topic symposium stated that cirrhotic patients should be screened for the presence of OV when portal hypertension is diagnosed [5]. Upper gastrointestinal (GI) endoscopy is the gold standard in the diagnosis of OV. It had been suggested for endoscopy to be repeated at 2-3 years interval in patients without varices and at 1-2 years interval in patients

with small varices to evaluate the development and / or progression of OV [3,6].

However, this approach has some limitations as endoscopy is an invasive procedure, the cost-effectiveness is questionable, also, only 9%-36% of patients with cirrhosis found to have varices on screening endoscopy [7]. So, the possibility of non-invasive means for identifying cirrhotic patients with OV or collateral presence is appealing, in that it could decrease the necessity of endoscopic screening with reduced healthcare costs [1].

Several parameters have been discussed along previous studies with varying rate of success. They have either been based on laboratory parameters, i.e. platelets count (PLTS) or ultrasonographic (US) features [8-12]. Recent studies explained the role of blood ammonia level (BAL) in the pathogenesis of portosystemic collaterals (PSC). Actually, ammonia levels cannot serve as a laboratory marker for portosystemic encephalopathy, being neither specific nor highly sensitive [13], although there may be a correlation with severity [14].

Our study aimed to determine noninvasive parameters for identifying the presence of OV, to compare the predictive accuracy of

these parameters in the development of OV and to evaluate the correlation between them and variceal size.

Patients and Methods

Study design

This cross-sectional study was carried out prospectively at Assiut University Hospital (AUH), Egypt. The study was approved by the local Ethics Committee of AUH and was conducted in accordance with the previsions of the Declaration of Helsiniki. Informed consent was obtained from all the participants before enrollment.

Patients

Sixty cirrhotic patients were selected from inpatient department and outpatient clinic of Internal Medicine and Tropical Medicine and Gastroenterology departments at Assiut University Hospital. All patients met the diagnostic criteria of liver cirrhosis by clinical, biochemical and ultrasonographic findings. The selected patients were of Child "A" and early "B" according to Child-Pugh scoring system [15].

These patients were divided into:

- 40 patients with evidence of esophageal varices by upper gastrointestinal endoscopy with or without abdominal portosystemic collaterals by abdominal ultrasound and
- 20 patients with neither evidence of varices (oesophageal or gastric) by upper gastrointestinal endoscopy nor portosystemic collaterals by abdominal ultrasound.

Exclusion criteria were patients who received endoscopic variceal ligation or sclerotherapy or beta blockers, presence of hepatic encephalopathy, active bleeding varices, chronic infection, hepatocellular carcinoma, portal vein thrombosis, renal insufficiency and blood disease.

All patients were subjected to the following:

- Thorough medical history and clinical examination
- Liver function tests; Aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, bilirubin and prothrombin time.
- Renal function tests: serum creatinine and blood urea nitrogen.
- Complete blood count including platelet count
- Fasting blood ammonia level (BAL).
- Abdominal ultrasonography to see size of liver and spleen, HCC, portal, splenic vein and longitudinal spleen (SPD) diameters, portal vein thrombosis, portosystemic collaterals and ascites.
- Upper gastrointestinal endoscopy to detect the presence of oesophageal and gastric varices, their size and number, and evidence of portal hypertensive gastropathy.

Methods

After avoidance of factors that may affect blood ammonia level (BAL), 5 ml of venous blood was taken in the morning and at complete rest from fasting patients. Blood samples were collected in tubes containing ethylene-diamine-tetraacetic acid (EDETA) and analyzed within 30 minutes of collection. BAL was estimated by enzymatic UV-method using the glutamate dehydrogenase reaction (GLDH-UV) with reagents obtained from (Greiner Diagnostic GmbH -Unter Gereuth 10 – D-79353 Bahlingen – Germany) according to the manufacturer's protocol.

	Patients with OV (n = 40)	Patients without OV (n = 20)
Age (years, mean ± SD)	52.2 ± 6.4	50.3 ± 6.1
Sex (n)		
Male	34 (85%)	11 (55%)
Female	6 (15%)	9 (45%)
Jaundice (n)	23 (57.5%)	4 (20)
Dilated abdominal veins (n)	5 (2%)	0
Hepatomegaly (n)	32 (80%)	6 (30%)
Splenomegaly (n)	37 (92.5%)	8 (40%)
Ascites (n)	3 (7.5%)	0
LPSS (n)	20 (50%)	0
Hb (gm/dl, mean ± SD)	9.7 ± 1.3	9.9 ± 1.6
WBCs (X103/dl, mean ± SD)	4.9 ± 1.7	5.5 ± 2
PLT (X103/dl, mean ± SD)	75.9 ± 17.4	76.3 ± 21.2
AST (IU/L, mean ± SD)	72.4 ± 25.1	78.1 ± 34
ALT (IU/L, mean ± SD)	77.8 ± 22.2	71.9 ± 18.1
Serum Albumin (gm/dl, mean ± SD)	2.9 ± 0.2	3 ± 0.2
Total bilirubin (mg/dl, mean ± SD)	2.1 ± 0.3	1.6 ± 0.3
INR (mean ± SD)	1.4 ± 0.1	1.3 ± 0.13
Gastric varices (n)	7	0
PHG (n)	32	0

OV: Oesophageal Varices; LPSS: Large Spontaneous Shunts; Hb: Hemoglobin; WBCs: White Blood Cells; PLT: Platelet Count; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; INR: International Normalization Ratio; PHG: Portal Hypertensive Gastropathy

Table 1: Demographic, clinical and laboratory characteristics of the study population.

Statistical analysis

All statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS) for Windows version 17 (SPSS Inc., Chicago, IL, USA). The quantitative data were expressed as mean ± standard deviation (SD) and were compared using Student's t-test. Qualitative data were expressed as percentage and compared using the chi-squared or Fisher's exact (two-tailed) test. The area under receiver operating characteristic curve (AUC) curves were plotted to measure and compare the performance of different non-invasive parameters in predicting presence of OV and to select the best cut-off value with the highest accuracy (by calculating the sensitivity, specificity, positive (PPV) and negative predictive values (NPV) positive likelihood ratio (+LR) for predicting or excluding OV. The relation between these parameters and size of OV was analyzed with the Spearman's

correlation coefficient test. For all analyses, p value < 0.05 was considered statistically significant.

Results

The baseline sociodemographic clinical and biochemical characteristics of the study patients were summarized in Table 1. The study included 60 patients with liver cirrhosis; 45 males (75%) and 15 females (25%) with mean age of 51.3 ± 6.3 years.

Table 2 showed that non-invasive parameters; blood ammonia level (BAL), spleen longitudinal diameter (SLD), portal vein diameter (PVD) and splenic vein diameter (PVD) were significantly higher means in patients with OV than patients without (P value < 0.001 for all). However, platelet count and platelet / SLD ratio, ALT, AST showed no significant differences between patients with and without OV (P value > 0.05).

non-invasive parameters (mean ± SD)	Patients with OV (n = 40)	Patients without OV (n = 20)	P value
Blood ammonia (µmol/L)	108.5 ± 32	50 ± 12	< 0.001
Spleen longitudinal diameter (cm)	16.1±1.4	13.5 ±1.6	< 0.001
Portal vein diameter (mm)	15.5 ± 1.3	10.4 ± 1.3	< 0.001
Splenic vein diameter (mm)	10.6 ±1.4	8.2 ± 0.5	< 0.001
Platelet count (X10³/dl)	75.9 ± 17.4	76.3 ± 21.2	0.245
Platelet / SLD ratio	4.7 ± 0.8	5.7 ± 1.2	0.231
AST (IU/L, mean ± SD)	72.4 ± 25.1	78.1 ± 34	0.499
ALT (IU/L, mean ± SD)	77.8 ± 22.2	71.9 ± 18.1	0.142

OV: Oesophageal Varices; SLD: Spleen Longitudinal Diameter; AST: Aspartate aminotransferase; ALT: Alanine Aminotransferase

Table 2: Comparison between patients with oesophageal varices and patients without regarding non-invasive markers.

The receiver operating characteristic (ROC) curve was done for blood ammonia level, SLD, PVD and SVD for the prediction of OV where it revealed that the PVD yielded the highest AUC (1.00), followed by the blood ammonia level (AUC = 0.99, 95% confidence interval (CI) = 0.99 - 1), SVD (AUC = 0.96, 95% CI = 0.94 – 1) and SLD (AUC = 0.77, 95% CI = 0.64 – 0.91) with P < 0.001 (for all), so all these variables were considered statistically significant (Figure 1).
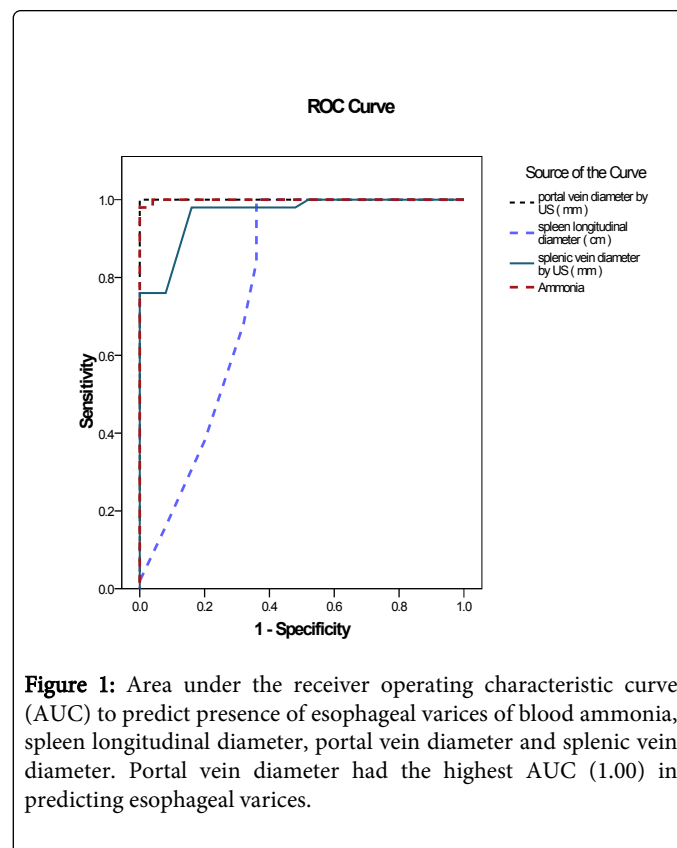

Figure 1: Area under the receiver operating characteristic curve (AUC) to predict presence of esophageal varices of blood ammonia, spleen longitudinal diameter, portal vein diameter and splenic vein diameter. Portal vein diameter had the highest AUC (1.00) in predicting esophageal varices.

The optimum cut-off values of the previously mentioned parameters to predict the presence of OV were illustrated in Table 3 where; PVD (13 mm) and BAL (65 µmol/L) showed the highest diagnostic indices followed by SLD (13.1 cm) and SVD (8.8 mm). All showed acceptable sensitivity (100% for all except 98% for SVD) and acceptable diagnostic accuracies (100%, 98%, 88%, and 82.3% respectively), blood ammonia showed higher (+LR) so it is ideal predictor for the presence of OV.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+	Accuracy (%)
Portal vein diameter (13 mm)	100	100	100	100	-	100
Blood ammonia level (65 µmol/L)	100	95	97.6	100	20	98
Spleen long diameter (13.1 cm)	100	65	85.1	100	2.9	88
Splenic vein diameter (8.8 mm)	97	82	91.5	93.2	5.4	82.3

PPV: Positive Predictive Value; NPV: Negative Predictive Value; LR+: Positive Likelihood Ratio

Table 3: Sensitivity, specificity, PPV, NPV LR+ and accuracy at optimum cut-off values of non-invasive parameters in predicting oesophageal varices.

Among different non-invasive parameters, only BAL positively correlated with the size of OV (r = 0.442, P = 0.002, Table 4).

Non-invasive parameters	Rho	P value
Blood ammonia level	0.442	0.002
Spleen longitudinal diameter	0.121	0.43
Portal vein diameter	0.103	0.44
Splenic vein diameter	0.132	0.31
Platelet count	-0.11	0.52
Platelet /SLD ratio	-0.11	0.47
AST	0.102	0.45
ALT	0.11	0.51
SLD: Spleen longitudinal diameter; AST: Aspartate aminotransferase; ALT: alanine aminotransferase		

Table 4: Correlation of non-invasive parameters and size of oesophageal varices.

Discussion

Oesophageal varices (OV) are the most relevant portosystemic collaterals (PSCs) and have the greatest clinical impact where variceal hemorrhage is associated with higher morbidity, mortality and hospital costs than other causes of upper gastrointestinal tract bleeding [16,17].

Our study assessed different non-invasive parameters to elaborate the reliable method to predict the presence of OV and their correlation with the variceal size.

The present work showed that blood ammonia level (BAL) was significantly higher in patients with OV than those without, where, BAL above 65 µmol/L can predict the presence of OV with 100% sensitivity, 95% specificity and 97.6% PPV. These results agreed with Tarantino et al., [1] who found that BAL more than 71 µmol/L had 97% sensitivity and 73% specificity for prediction of presence of portosystemic shunts. In addition, Khondaker et al., [18] revealed that blood ammonia at 63µmol/L had 95% sensitivity and 50% specificity in detecting large OV in cirrhotics suggesting its usefulness in identifying patients with large varices who need endoscopy.

Our findings were consistent with Schepis et al. [19] and Cottone et al. [20], as we revealed that PVD is an independent factor for prediction of the presence of OV, as patients with OV showed statistically significant higher mean of PVD in comparison to patients without varices. Also, PVD ≥ 13 mm had 100% sensitivity in predication of OV. Unlike Sarwar et al. [21] who postulated that PVD > 11 mm on ultrasonography is independently associated with the presence with OV.

Spleen longitudinal diameter (SLD) had significantly higher mean in patients with OV in comparison to patients without varices. SLD ≥ 13.1 cm had 100% sensitivity and 65% specificity for the prediction of the presence of OV. These findings agreed with Thomopoulos et al. [22] who proved that SLD of 13.5 cm or more has 95% sensitivity and 37% specificity in prediction of the presence of OV so, it can be considered as a good predictor for the presence of varices.

The current study showed that SVD was significantly wider in patients with OV than those without. SVD of 8.8 mm or more was a good predictor for the presence of OV with 97% sensitivity and 82% specificity. This was matched to findings of Montasser et al. [23] who found that splenic vein diameter ≥ 8.9 mm can predict the presence of OV in cirrhotics with 98% sensitivity and 84% specificity.

In agreement with Qamar et al. [24], platelets and platelets / splenic longitudinal diameter (PLT/SLD) ratio did not show significant difference in patients with and without OV suggesting that these markers cannot predict the presence of varices. However, this finding was in contrast to several studies done by Tarantino et al. [1] and Zaman et al. [9]. In this work, patients of Child "A" and early "B" liver cirrhosis had less impairment of platelet count which may explain this conflict.

Among these non-invasive parameters, only BAL positively correlated with the size of OV. This finding was comparable with that reported by Tarantino et al., [1] where r= 0.43 and P value was < 0.001. On the other hand, our results were consistent with previous studies reported that the other markers did not show any correlation with the size of varices [18].

This study was a single-center and limited to patients with early liver cirrhosis. In addition, our findings are needed to be confirmed by further multicenter studies and to determine whether these parameters will be of benefit for the more severely affected patients who are unable to do endoscopic screening.

In conclusion, BAL, PVD, SVD and SLD were good non-invasive predictors for the presence of OV in cirrhotics with the superiority of PVD and ammonia. BAL could be a good tool to identify patients with large oesophageal varices, so, pinpoint those patients requiring closer follow-up and endoscopic screening.

Conflicts of interest

The authors declared that they had no conflicts of interest concerning this article.

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