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Non-Invasive Assessment of Esophageal Varices in Cirrhotic Yemeni Patients

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ABSTRACT

Objectives: *To study the effectiveness of 6 non-invasive methods in the evaluation of the presence of esophageal varices in chronic liver disease (CLD) in Yemeni patients.* ***Design:*** *Prospective study of patients with chronic liver disease evaluated for presence or absence of esophageal varices by using non-invasive tests.* ***Setting:*** *Specialized center of gastrointestinal and liver diseases in Ibb city, Yemen.* ***Subjects:*** *Consecutive patients with clinical and para-clinical criteria of CLD with no upper GIT bleeding at presentation or in their past history were included in this study during the period from July 2017 to December 2017.* ***Results:*** *During the study period, 103 patients with CLD fulfilled the including criteria and were enrolled in this study, 60 of them were males and 43 were females. The age ranged between 16 years and 81 years and the mean age was 42.69 ± 16.96 years. Of these 103 patients, 62 cases (59.95%) had esophageal varices, 36 (58%) were small and 26 (42%) were large. The sensitivity, specificity, PPV, and NPV of 6 studied para-clinical and biochemical variables were evaluated. The sensitivity and the specificity for spleen diameter was 79.7% and 33.3% respectively, for platelet count 26.6% and 87.2%, for P.V diameter 39% and 47.4%, for Rt. lobe diameter/albumin ratio 23.4% and 82%, for spleen diameter/platelet count ratio 37.5% and 74.4% and for AST/ALT ratio 53.1% and 51.3%.* ***Conclusion:*** *No one of the studied non-invasive tests had high predictive value or high sensitivity or specificity for prediction of esophageal varices, consequently upper GIT endoscopy is still the gold standard way in the diagnosis and grading of esophageal varices.*

Keywords: Esophageal varices, Non-invasive tests, CLD, Yemen

INTRODUCTION

Liver cirrhosis (LC) is the final evaluative stage of any chronic liver disease, resulting in the formation of fibrous tissue, disorganization of liver architecture, and nodule formation, which interferes with liver function and results in portal hypertension [1,2]. The three primary complications of portal hypertension are gastroesophageal varices with potential rupture and hemorrhage, ascites, and hypersplenism [2]. Esophageal varices develop in the context of increased portal blood pressure owing to increase portal vascular resistance. The hypertensive portal vein is decompressed by diverting up to 90% of the portal flow through portosystemic collaterals back to the heart, resulting in enlargement of these vessels [3]. These vessels are commonly located at the gastroesophageal junction, where they lie subjacent to the mucosa and present as gastric and esophageal varices [3]. Esophageal varices are present in approximately 50% of cirrhotic patients at their initial diagnosis, being more common in advance stage chronic liver disease (CLD), Child-Pugh class C patients compared to early-stage Child-Pugh class A patients (85% versus 40%) [4-6]. Once varices form, they enlarge from small to large at a rate of 5-12% per year and bleed at a rate of 5-15% per year [4,7]. The greatest bleeding risk is seen in large varices classified as being more than 5 mm diameter and is also influenced by liver disease severity as assessed by the Child-Pugh score, and by the presence of red wale markings on varices at endoscopy [8,9]. Therefore, these factors should also be taken into consideration to classify "high-risk varices" [1,8]. Up to 25% of patients with newly diagnosed varices will experience variceal bleeding within 2 years [5]. Mortality per bleeding episode is around 10-20% [9,10], and one-year survival is only 63% [11]. Therefore, screening for EV in liver cirrhosis patients is a strong recommendation in all consensus statements [12-14].

Current guidelines recommend that all cirrhotic patients should be screened for varices at initial diagnosis, with follow up every 2-3 years for patients without varices (depending upon liver disease severity) and 1-2 years for patients with small varices, to assess for enlargement of varices and need for prophylactic treatment [15]. Upper GI endoscopy remains the gold standard for screening, but this test is not without its own limitations as it is invasive, high cost and poorly accepted by patients. If it were possible to predict esophageal varices by non-invasive means this would restrict testing to the population deemed to be at most risk and reduce the number of endoscopies required. Such a screening test should be simple, quick, reproducible, and cost-effective. Several studies have evaluated possible non-invasive markers of esophageal varices in patients with cirrhosis [16-23]. However, the findings of these previous studies are controversial and their utility in clinical practice is uncertain. Several studies in the past have shown independent parameters like platelet count, splenomegaly, advanced child status, serum albumin, and high portal vein diameter at ultrasonography to be useful for this purpose [24-33]. Giannini, et al., proposed the platelet count/spleen diameter ratio of ≤ 909, as an accurate non-invasive marker for the presence of esophageal varices [17]. Such predictive factors may be expected to vary in different populations because of differences in the etiology of liver cirrhosis, the severity of liver disease and nutritional status, and the sensitivity and specificity vary widely at different studies [34,35]. Data on this aspect in Yemeni patients are absent.

Objectives

To evaluate the utility of various clinical, biochemical, and ultrasonographical parameters for predicting the presence of esophageal varices of liver cirrhosis in Yemeni patients.

PATIENTS AND METHODS

Patients

Our study sample was CLD patients prospectively collected from the private center of Gastroenterology and Hepatology at Ibb city in the period between July 2017 and December 2017. Patients with active bleeding, acute hepatic failure, portal vein thrombosis, hepatic focal lesions and those who had undergone previous endoscopic sclerosis, band ligation of esophageal varices or splenectomy were excluded from the study. In total, 103 individuals diagnosed with CLD completed the needed data and were enrolled in this study.

Method

The diagnosis of the chronic liver disease was based on the history of more than 6 months and physical examination, as well as by standard laboratory and sonographic data consistent with CLD. History included details on the duration of jaundice, ascites, oliguria, pedal edema, spider navi, gastrointestinal bleeding. Presence or absence of ascites, splenomegaly, and hepatic encephalopathy were noted. CBC, LFTs including serum bilirubin, albumin/globulin ratio, transaminases, and prothrombin time, were estimated. Modified Child-Turcotte-Pugh (CTP) class was calculated for each patient. Special investigations included HBsAg (Hepatitis B Virus Surface Antigen), anti-HCV antibody assay, antinuclear antibody, anti-smooth muscle antibody and anti-mitochondrial antibody assays and for selected patients slit lamp examination, serum Ceruloplasmin and iron studies were done.

All patients also underwent ultrasonography by the same expert doctor using (LOGIQ9) of the upper abdomen including measurement of spleen diameter, portal vein diameter, right liver lobe diameter and the presence of ascites.

An upper GIT endoscopy was performed in a single endoscopy unit using (PENTAX-EPK-5000 Unit) and the data regarding presence or absence of esophageal or gastric varices, grading of the varices and other endoscopic findings were registered.

The esophageal varices were grading into small and large varices based on the criteria proposed at the Baveno I Consensus Conference [36]. The small grade was defined as esophageal varices flattening with insufflation or minimally protruding into the esophageal lumen (i.e., Paquet's grades I-II), while the large grade was defined as esophageal varices obviously protruding into and filling at least 50% of the esophageal lumen (i.e., Paquet's grades III-IV) [36]. We studied portal vein diameter, spleen bipolar diameter, platelet count, platelet count (109/L)/spleen diameter (mm) ratio (SPRI), Rt. Lobe/albumin ratio and AST/ALT ratio at the following cut off points; portal vein diameter at 14 mm, spleen bipolar diameter at 12 cm, Platelet count at 100x109/L, SPRI at 909, Rt. Lobe/albumin ratio at 4.4 and AST/ALT ratio at 1.1.

Statistical Analysis

The statistical analysis was performed using the SPSS software version 20.0 (SPSS Inc. Chicago, IL, USA). The continuous variables were presented as mean values and standard deviation. The data were compared using the chi-square test. The diagnostic performance of our variables was assessed using sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

RESULTS

A total of 103 consecutive patients were studied, 60 were males (58.3%) and 43 were females (41.7%). The age ranged between 16-81 years. The mean age of the patients was 42.69 ± 16.96 years (Table 1).

Table 1 Distribution of the cases according to the gender and the age

Age in years	Male		Female		Total	
	n	%	n	%	n	%
Less than 20	11	18.3%	0	0. 0%	11	10.7%
21-40	24	40.0%	17	39.5%	41	39.8%
41-60	14	23.3%	21	48.9%	35	33.9%
>60	11	18.3%	5	11.6%	16	15.5%
Total	60	100.0%	43	100.0%	103	100.0%

The etiology of liver cirrhosis was pre-determined at diagnosis and mainly included viral causes in 30 cases (29.1%) of which 24 (23.3%) cases were of hepatitis C viral (HCV) infection, and 6 cases (5.8%) were of hepatitis B viral (HBV) infection. The non-viral etiology was found in 75 cases (72.8%) in which autoimmune cause was present in 22 (21.4) cases, autoimmune-like (khat induced) in 41 (39.8%) cases, primary biliary cirrhosis in 2 (1.9%) cases, hemochromatosis in one case and in 9 cases (8.7%) the etiology was not known. There was no statistically significant difference in disease etiology between the patients with esophageal varices and patients without esophageal varices (p=0.128). The clinical presentations in our patients and their clinical and para-clinical variables and their correlation with the presence of the esophageal varices are shown in Table 2. The variables that had statistically significant difference were found in sex and Child-Pugh score (p=0.000 in both), where EV was found to be more in males and Child class C more than B and A.

Table 2 Clinical and para-clinical variables of the study sample in relation with E.V

Variable	Presence of esophageal varices		Total	p-value
	No	Yes		
	No. (%)	No. (%)		
Male/Female	15 (25)/26 (60.5%)	45 (75%)/17 (39.5%)	60 (100%)/43 (100)	0
Age	38 (18-65%)	52 (16-81%)	40 (16-81)	0.09
Ascites	9 (25%)	27 (75%)	36 (100)	0.025
Spleen bipolar diameter (mm)*	123 (70-170%)	130 (95-200%)	132 (70-200)	0.561
Child-Pugh score				
A	29 (63%)	17 (37%)	46 (100)	-
B	10 (25%)	29 (74.4%)	39 (100)	-
C	2 (11%)	16 (89%)	18 (100)	-
Epistaxis	21 (47.7%)	23 (52.3%)	44 (100)	0.165
Jaundice	24 (43.6%)	31 (56.4%)	55 (100)	0.395
L.L oedema	8 (24.2%)	25 (75.8%)	33 (100)	0.027
Spider navi	3 (23.1%)	10 (76.9%)	13 (100)	0.187
Flapping tremor	12 (48%)	13 (52%)	25 (100)	0.336
Itching	13 (44.8%)	16 (55.2%)	29 (100)	0.515
Fatigue	35 (40.2%)	52 (59.8%)	87 (100)	0.838
Hemoglobin (g/dl)*	13 (7.8-16%)	13 (7.5-17.5%)	13 (7.5-17.5)	0.142
S bilirubin (mg/dl)*	2.5 (7-27%)	1.5 (5-33%)	1.5 (5-33)	0.486
S albumin (g/dl)*	3.6 (2.5-4.2%)	3.6 (1.8-4.2%)	3.6 (1.8-4.2)	0.567
Platelet count (per µl)	6 (27.3%)	16 (72.7%)	22 (100)	0.176

Splenomegaly>120mm	39 (42.9%)	52 (57.1%)	91 (100)	0.326
Portal vein diameter >14mm	7 (29.2%)	17 (70.8%)	24 (100)	0.208
Platelet count/ spleen diameter ratio<909	11 (31.4%)	24 (68.6%)	35 (100)	0.192
AST/ALT ratio>1.1	25 (41%)	36 (59%)	61 (100)	0.702
Rt lobe diameter/Albumin ratio> 4.4	7 (35%)	13 (65%)	20 (100)	0.597
*Median (minimum-maximum)				

Of these 103 studied patients, 62 (59.2%) had esophageal varices, of them, 36 (58%) were small varices (grade I and II) and 26 (42%) were large (grade III and IV) (Table 3).

Table 3 Causes of CLD and relation to the presence of esophageal varices in both sexes

Etiology			Presence and grades of EV	Sex				Total	
				Male		Female			
				No	%	No	%	No	%
Viral	No	%	No varices	2	14.3%	7	43.8%	9	30.0%
	-	-	Grade I EV	2	14.3%	1	6.3%	3	10.0%
	-	-	Grade II EV	2	14.3%	4	25.0%	6	20.0%
HCH	22	21.4%	Grade III EV	8	57.1%	4	25.0%	12	40.0%
	-	-	Grade VI EV	0	0.0%	0	0.0%	0	0.0%
HBV	6	5.8%	**Total**	14	100.0%	16	100.0%	30	100.0%
Non-viral	-	-	No varices	13	28.3%	19	70.4%	32	43.8%
AIH	22	21.4%	Grade I EV	8	17.4%	2	7.4%	10	13.7%
Khat induced	41	39.8%	Grade II EV	11	23.9%	6	22.2%	17	23.3%
PBC	2	1.9%	Grade III EV	13	28.3%	0	0.0%	13	17.8%
Others(hemo-chromatosis, Unknown)	10	9.7%	Grade VI EV	1	2.2%	0	0.0%	1	1.4%
			Total	46	100.0%	27	100.0%	73	100.0%
Total	103	100.0%	-	60	100.0%	43	100.0%	103	100.0%

The sensitivity, specificity, PPV, and NPV of each of the 6 studied variables are shown in Table 4. The range of sensitivity was between 23.4%-79.7% in which the highest sensitive test was spleen diameter, the range of specificity was between 33.33%-87.2% in which the highest specificity was seen in platelet count, the range of PPV was 64.2%-77.3%, and the range of NPV was between 39.5%-50% (Table 4).

Table 4 Sensitivity, specificity, PPV and NPV in our studied parameters

Parameter	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Spleen diameter	79.69%	33.33%	66.23%	50.00%
AST/ALT ratio	53.13%	51.28%	64.15%	40.00%
Rt. lobe diameter/Albumin ratio	23.44%	82.00%	68.18%	39.50%
PV diameter	39.00%	47.36%	71.43%	42.65%
Platelet count	26.56%	87.18%	77.27%	41.98%
SPRI	37.50%	74.35%	70.58%	42.00%
PPV=positive predictive value; NPV=negative predictive value; AST=aspartate transaminase; ALT=Alanine transaminase; PV=portal vein; SPRI=platelet count/spleen bipolar diameter ratio				

DISCUSSION

Esophageal varices are a dangerous clinical consequence of CLD. Since variceal screening causes considerable endoscopic burden and cost, seeking a less expensive, noninvasive means for accurate prediction of esophageal varices has great clinical importance. The promising predictive marks have been focusing on common laboratory variables such as platelet count, LFT and albumin level, ultrasound parameters such as spleen and portal vein dimension.

We studied 103 cases, 60 (58.3%) were males and 43 (41.7%) were females. The mean age of the patients was 42.69 ± 16.96 years (Table 1). The causes of liver disease were viral in 28 cases (27.2%) and non-viral in 75 cases (72.8%). Among viral etiology in our study, HCV was responsible for the majority of them in 24 of cases (23.3%); meanwhile HBV encountered in only 6 cases (5.8%) (Table 2). One of the explanations for this small HBV cases and large

HCV cases in our studied sample may be the fact that Ibb governorate where this study was conducted has one of the highest prevalence rates of HCV infection in the country which may reach 4.2% [37]. Meanwhile in the capital Sana'a the prevalence was of 2.2% and in Aden, it was of 0.6% [38]. Another explanation may be the gradual decrease in the prevalence of HBV since the introduction of HBV vaccine in the vaccination program [39,40]. The 72.8% of the non-viral causes mainly included khat induced hepatitis (autoimmune-like) in 39.8%, autoimmune liver disease in 23.3% of the cases, a case of hemochromatosis and 9 cases (8.7%) were of unknown etiology (Table 2). Khat chewing is a very common social habit in Yemen and Eastern African countries for its psycho-stimulant and euphoric effects [40,41]. These effects are attributed to its alkaloid compounds which include cathinone, and to a lesser degree, cathine, and norephedrine [40,41]. In recent literature and case reports, khat chewing is incriminated to be a cause of severe non-viral liver disease which by its evolutional course, clinical, and para-clinical features and response to immunosuppressive treatment is similar to AIH but it mainly affects heavy khat chewer young adult males [40,41].

Of our 103 studied patients, 41 (39.8%) had no esophageal varices, 36 (35%) had small esophageal varices and 26 (25.3%) had large esophageal varices (Table 2). In general, there were no statistically significant differences in the presence of esophageal varices between viral and non-viral causes. However, esophageal varices affect males more than females whatever the cause of CLD (Table 2).

In this study, 3 individual and 3 compound parameters were evaluated. We measured the sensitivity, specificity, PPV, and NPV for every parameter. No single parameter was found to offer a self-sufficient predictive function for esophageal varices. Moreover, a combination of multiple parameters (platelet count, spleen, Rt. Lobe diameter, albumin, AST, and ALT) did not significantly improve the predictive accuracy in our studied patients. Several studies suggest that platelet count may predict the presence of EV in patients with cirrhosis [42-44]. However, the discriminating threshold for the presence of varices varies widely, ranging between 68,000 and 160,000/mm^3 [44]. The sensitivities for thrombocytopenia fluctuate from 62% to 100%, and the specificities range from 18% to 77% [45]. In our study, at a cut-off point of 100 x 106 platelet count sensitivity, specificity was of 26.56%, 87.18%, respectively. This wide range of sensitivities and specificities may be explained by using a different cut off points and the different etiology of CLD in different studies. In an attempt to improve the predictive value of the platelet count, it has been combined with spleen bipolar diameter but without significant improvement in the predictive accuracy as the sensitivity of platelet count/spleen diameter ratio was only of 37.5%, the specificity was of 74.35%, the PPV was of 70.58% and the NPV was of 42%. These results of ours are discordance with the early results of Giannini, et al., study in which at the same cut-o□ value of 909, they reported a PPV of 96% and NPV of 100% [17]. Unfortunately, despite promising early results by Giannini, et al., the platelet count/spleen diameter ratio in our study was not found to be a reliable tool to screen for esophageal varices.

Spleen longitudinal diameter had a sensitivity and specificity, of 79.6% and 33.3%, respectively and this is not in the agreement with Homopolar, et al., and Hassan, et al., which reported a sensitivity and specificity [45,46]. Rt. lobe/ albumin ratio has been assessed in a single study of 94 cirrhotic patients by Alempijevic, et al., at a cut-o□ value of 4.4, this gave a sensitivity of 83.1% and specificity of 73.9% [47], and the results of our study was in concordance with it regarding specificity which represented 82%, meanwhile the sensitivity was much lower at 23.4% (Table 4).

Finally, we evaluated some clinical and para-clinical variables in correlation with the presence of esophageal varices and the only variable which had a statistically significant difference was a Child-Pugh score (Table 3). This result regard Child-Pugh is in concordance with what is known in the global medical literature [2,5].

CONCLUSION

Non-invasive tests for prediction of esophageal varices are not sensitive and/or specific enough to avoid screening upper GI endoscopy in CLD patients.

LIMITATIONS

This was a single center study, raising the question of generalizability. Larger studies on larger groups of patients are needed to confirm the results and to study other parameters or the same parameters at different cut-off points determined statistically in our patients who may be more representative for our community.

DECLARATIONS

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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