Laboratory and Ultrasonographic predictors of oesophageal varices in cirrhotic patients

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ABSTRACT.

Portal hypertension in cirrhosis results from progressive fibrotic remodeling of the liver, which increases the resistance to hepatic sinusoidal blood flow. Increased portal venous pressure causes esophageal and gastric varices, which contribute substantially to cirrhosis-related morbidity and mortality.

The gold standard in the diagnosis of varices esophagogastroduodenoscopy (EGD) but identification of non –invasive predictors of oesophageal varices (OVs) will allow upper gastrointestinal (GIT) endoscopy to be carried out only in selected group of patients **.**

Different non-invasive parameters including clinical, laboratory and sonographic predictors were suggested an alternative approach to perform selective screening endoscopy only in patients at high risk.

Objective: Our objective is to evaluate whether the NIHCED (non-invasive hepatitis C related cirrhosis early detection) score and the right lobe diameter to albumin ratio can predict the presence of esophageal varices in patients with liver cirrhosis.

Patients and method: This prospective study included seventy-five patients with liver cirrhosis, all patients were evaluated clinically and ultrasonographically. complete blood count, liver function tests, calculation of NIHCED score and right lobe diameter to albumin ratio. Upper GIT endoscopy were done to all of them for detection of oesophageal varices.

Results In total 75 patients were included (51 males and 24 females) with mean age 53.11±9.89. All 75 patients were segregated into two groups those with oesophageal varices and those without oesophageal varices.

Roc curve analysis of NIHCED score was applied to both goups with a cut off score of >45. It had a sensitivity of 70%, specifity of 78%, and diagnostic accurancy of 74% with an AUC of 0.77 (95% CI, 0.66-0.86).

Roc curve analysis of right lobe diameter to albumin ratio was applied to both groups with a cut off score of >2.80. It had a sensitivity of 80%, specifity of 53%, and diagnostic accurancy of 67% with an AUC of 0.67 (95% CI , 0.55-0.77).

Conclusions: The NIHCED score and right lobe diameter to albumin ratio were simple non-invasive predictors of presence of varices in patients with liver cirrhosis.

Key words: Liver Cirrhosis, **oesophageal varices**.
Predictive index. NIHCED index.

INTRODUCTION:

Liver Cirrhosis is a diffuse process characterized by tissue fibrosis and the conversion of normal liver architecture into structurally abnormal nodules and endothelial fenestrations are lost, a process termed sinusoidal capillarization **(1).** Portal hypertension is a clinical syndrome defined by a Portal venous pressure gradient exceeding 5 mmHg. Cirrhosis is the most common cause of portal hypertension in the Western world **(2).**

Portal hypertension results in the development of esophagogastric varices which often bleed; and pla ys a role in the development of ascites, hepatorenal syndrome and hepatic encephalopathy. Portal hypertension and resulting portosystemic collaterals may also be responsible for the cardiopulmonary complications like porto-pulmonary hypertension and hepatopulmonary syndrome **(3).**

Identification of non –invasive predictors of OVs will allow upper gastrointestinal tract(GIT) endoscopy to be carried out only in selected group of patients thus avoid un-necessary intervention and at the same time not to miss patients at risk of bleeding **(4).**

To date, several predictive markers for presence of varices in-patient with liver cirrhosis include clinical, laboratory, and echographic data have been published. In our study, we validated the Sabadell NIHCED (non-invasive hepatitis C related cirrhosis early detection) index, it includes several demographic, laboratory and echographic parameters, also we validated the right lobe diameter to albumin ratio.

Patients and methods:

Between from October 2016 to September 2017, 75 cirrhotic patients were prospectively and consecutively recruited from Tropical Medicine and Gastroenterology Department, Sohag University Hospital

Inclusion criteria:

Patients with liver cirrhosis (clinically or sonographically proved) with no history of upper gastrointestinal bleeding.

Exclusion criteria:

- Patients known to have esophageal varices
-Patients who refuse endoscopic examinations .
-History of previous upper gastrointestinal bleeding.

Ethical consideration:

We got approval of Sohag Faculty of Medicine Ethical Committee.All patients signed an informed written consent before starting data collection with respect to patient's confidentiality.

Methods of the study:

Each patient included in the study was subjected to:

§ **Complete history taking and physical examination**.

§ **Laboratory investigations**: Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), serum alkaline phosphatase, serum albumin, prothrombin time and concentration, total & differential bilirubin, hepatitis markers for HBV and HCV, blood sugar, Haemoglobin level (Hb) and serum creatinine.

§ **Assessment of the severity of liver diseases using the Child-Pugh score (5)**: Three laboratory tests (bilirubin, albumin, and prothrombin time), combined with the presence and severity of encephalopathy and ascites, are included in the Child-Pugh score. The Child-Pugh score is given by the sum of the score (1 to 3) of each of the five parameters. A score of 6 or lower defines the patient as class A، 7 to 9 as class B, and 10 or higher as class C.

§ **Abdominal ultrasonography**.

-To evaluate liver (size, echogenicity and any focal lesion), portal vein, spleen, portosystemic collaterals, and detect ascites.

- Right lobe diameter (Right hepatic lobe atrophy (longitudinal diameter < 9 cm).

-Caudate lobe diameter (Hypertrophy of the caudate lobe (diameter > 4 cm)

§ **NIHCED score:-**as shown in table 1, according to *Bejarano et al (6).*

Table (1): compenents of NIHCED score as described by *Bejarano et al (6).*

Variable	Point score
Age ≥60	13 points
Prothrombin time ≥1,1	10 points
Platelets ≤100,000	15 points
AST/ALT≥1	10 points
Caudate lobe hypertrophy	6 points
Right hepatic lobe atrophy	15 points
Splenomegaly	7points

§ **Upper GIT endoscopy:**

Upper GIT endoscopy was done for all patients for detection of number, site, and size of varices, presence of red color sign.

Statistical analysis

Quantitative data was represented as mean, standard deviation, median and range. Data was analyzed using student t-test to compare means of two groups. When the data was not normally, distributed Mann-Whitney test was used to compare two groups. Qualitative data was presented as number and percentage and compared using either Chi square test or fisher exact test. Graphs were produced by using Excel or STATA program. Multivariate logistic regression analyses were used to determine factors predict mortality in-patient with VAH. Data were analyzed by sensitivity, specificity, positive, and negative predictive value derived from the receiver operating characteristic (ROC) curve. The diagnostic accuracy of different prognostic scores was expressed as the area under the ROC curve (AUC). Statistical analysis was performed using Medcalc for Windows (version 11.0) and STATA (version 9.2). P value was considered significant if it was less than 0.05.

Results

Among the 75 patients included in this study, 47 patients had esophageal varices (63%).

All 75 patients were categorized into two groups according to findings in oesophagogastroduodenoscopy (EGD): Group (A) 28 patients without esophageal varices (37%), Group (B) 47patients with esophageal varices (63 %).

As regard sonographic data , splenomegaly, caudate lobe hypertrophy, Right hepatic lobe atrophy, collaterals and dilated splenic vein were significantely more frequent in patients with oesophageal varices (p=0.01, P=0.003, P=<0.0001, P=0.02, P=0.04) as shown in table (2) .

Table (2): ultrasonogaphic results of the studied group.

Characteristics	Group A N 28	Group B N 47	P value
Rt.lobe diameter (cm)			
Mean ± SD	10.20±2.04	10.38±2.03	0.71
Median (range)	10 (7-15.5)	10 (8-17)	
Right hepatic lobe atrophy			
No	20 (71.43%)	10 (21.28%)	**<0.0001**
Yes	8 (28.57%)	37 (78.72%)	
Caudate lobe diameter(cm)			
Mean ± SD	3.63±1.06	4.29±0.85	**0.007**
Median (range	3.5 (2-5.5)	4.5 (2-6)	
Caudate lobe hypertrophy			
No	16 (57.14%)	11 (23.40%)	**0.003**
Yes	12 (42.86%)	36 (76.60%)	
PV diameter (mm)			
Mean ± SD	11.08±2.47	11.99±2.99	0.18
Median (range)	10 (7-17)	11 (7-18)	
Collaterals			
No	28 (100%)	39 (82.98%)	**0.02**
Yes	0	8 (17.02%)	
Splenic vein			
Not dilated	28 (100%)	40 (85.11%)	**0.04**
Dilated	0	7 (14.89%)	
Ascites (by US)			
No	21 (75.00%)	29 (61.70%)	0.24
Yes	7 (25.00%)	18 (38.30%)	
Splenomegaly(by US)			
No	12 (42.86%)	8 (17.02%)	**0.01**
Yes	16 (57.14%)	39 (82.98%)	

Patients with esophageal varices had significantly lower value of platelet and Albumin than those without OVS (figures 1, 2)
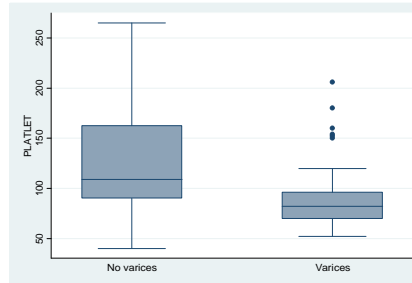

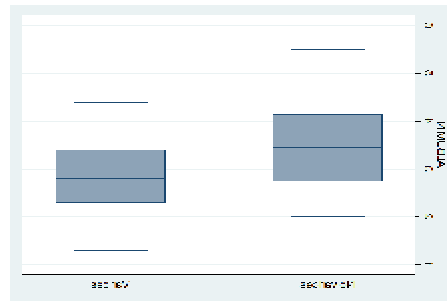**Figure (1) Comparison between patients without and with varices as regards Platelet count.**

Figure (2) Comparison between patients without and with varices as regards serum albumin

Analysis of NIHCED score as a predictor of esophageal varices in cirrhotic patients

All 75 patients were segregated into two groups those with esophageal varices and those without OVS.

Table (3) summarizes the labratory and echgraphic data included in the NIHCED score.
Roc curve analysis was applied to both goups with acut off score of >45.It had a sensitivity of 70%, specifity of 78%, and diagnostic accurancy of 74% with an AUC of 0.77 (95% CI, 0.66-
0.86) (Table 4, figure 3)

**Table (3) laboratory and echographic data included in the NIHCED score.**

Variables	Group (A) N 28	Group (B) N 47	P value
Age ≥60			
No	19 (67.86%)	34 (72.34%)	0.68
Yes	9 (32.14%)	13 (27.66%)	
Prothrombin time≥1.1			
No	22 (78.57%)	36 (76.60%)	0.84
Yes	6 (21.43%)	11 (23.40%)	
Platelets ≤100,000			
No	15 (53.57%)	9 (19.15%)	**0.002**
Yes	13 (46.43%)	38 (80.85%)	
AST/ALT≥1			
No	11 (39.29%)	4 (8.51%)	**0.001**
Yes	17 (60.71%)	43 (91.49%)	
Caudate lobe hypertrophy			
No	16 (57.14%)	11 (23.40%)	0.003
Yes	12 (42.86%)	36 (76.60%)	
Right hepatic lobe atrophy			
No	20 (71.43%)	10 (21.28%)	**<0.0001**
Yes	8 (28.57%)	37 (78.72%)	
Splenomegaly			
No	12 (42.86%)	8 (17.02%)	**0.01**
Yes	16 (57.14%)	39 (82.98%)	
NIHCED score			

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Mean ± SD	30.21±20.53	49.43±16.34	**0.0001**
Median (range)	26.5 (0-76)	53 (10-76)	

Table (4) Area under the curve, sensitivity, specificity, positive predictive value, negative predictive

value and accuracy of NIHCED score in predicting oesophageal varices.

Variable	Cut off point	AUC (95% CI)	Sensitivity	Specificity	PPV	NPP	accuracy	P value
NIHCED score	**>45**	**0.77 (0.66-0.86)**	**70.2**	**78.6**	**84.6**	**61.1**	**74.4**	**<0.00011**
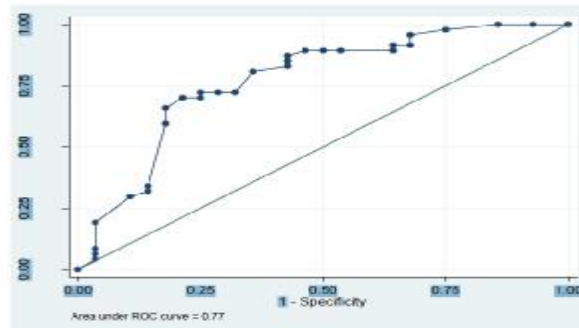
**Figure (3): Roc curve analysis of NIHCED score in predicting oesophageal varices.**

Right lobe diameter to albumin ratio as predictorof esophageal varices.
There was a significant association between right lobe diameter toalbumin ratio and presence of varices, Patients with no varices had a mean ratio of (3.16±1.17), whereas Patients with varices had a mean ratio of (3.90±1.37) (P value =0.02)
Roc curve analysis was applied to both groups with acut off score of >2.8. It had a sensitivity of 80% , specifity of 53%, and diagnostic accurancy of 67% with an AUC of 0.67(95% CI, 0.55-0.77) as shown in (table 5, figure 4)

Table (5) Area under the curve, sensitivity, specificity, positive predictive value, negative predictive value and accuracy of right lobe diameter to albumin ratio in predicting varices,

Variable	Cut off point	AUC (95% CI)	Sensitivity	Specificity	PPV	NPP	accuracy	P value
Rt. lobe D/albumin ratio	>2.80	0.67 (0.55-0.77)	80.9	53.6	74.5	62.5	67.3	0.01
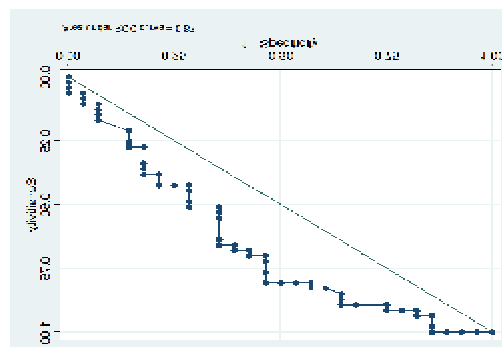
Figure (4) Roc curve analysis of right lobe diameter to albumin ratio in predicting varices.

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Discussion:

Liver cirrhosis is the pathologic outcome of many chronic liver diseases, in which repeated injury to the liver results in fibrosis, scarring, and ultimately functional impairment **(7)**.

Portal hypertension commonly accompanies liver cirrhosis with the development of esophageal varices (OVS) and portal hypertensive gastropathy (PHG) as major complications **(8)**.

In this study, we evaluated the role of NIHCED score and right lobe diameter to albumin ratio in predicting the presence and grade of esophageal varices in cirrhotic patients admitted to our hospital with no history of previous gastrointestinal bleeding.

We found that a decrease in platelet count and serum albumin level were significantly associated with the presence of esophageal varices in cirrhotic patients (P=0.001, P=0.007). The Pathogenesis of thrombocytopenia includes productive, consumptive or distributional mechanisms. It is commonly believed to be due to pooling and destruction of platelets in the spleen, which may be mediated by platelet-associated IgG. Reduced levels of thrombopoeitin either due to impaired production or rapid degradation may also add to thrombocytopenia. The pathogenesis of low albumin level in patients with esophageal varices is that synthesis is decreased because of the loss of hepatic cell mass. Also, portal blood flow is often decreased and poorly distributed, leading to maldistribution of nutrients and oxygen. The flow of substrate may affect certain functions of the liver, including protein synthesis **(9,10).**

Our results agree with **Mandal et al. (11)** who reported that platelet count and albumin are reliable predictors of variceal hemorrhage .These finding

are in accordance with those of **Farooqi et al. (12)** who found that platelet count of < 65 x 103/μL, serum albumin <2.2 g/dl are independent predictors of esophageal varices on endoscopy.

We found that splenomegaly was significantly associated with the presence of esophageal varices in cirrhotic patients. The pathogenesis of splenomegaly in patients with OVS is that splenomegaly is not only caused by portal congestion, but it is mainly due to tissue hyperplasia and fibrosis. The increase in spleen size is followed by an increase in splenic blood flow, which participates in portal hypertension **(13).**This finding correlates with the study carried out by **Dib et al. (14)** who reported that spleen length is an independent predictor of esophageal varices.

In This study we found that ultrasonographic findings such as Caudate lobe hypertrophy , collaterals were significantly associated with esophageal varices .The pathogenesis of caudate lobe hypertrophy in patients with OVS is that caudate lobe is anatomically distinct from the left and right lobes as it has its own portal veins, hepatic arteries, hepatic veins .The short intrahepatic course of the caudate lobe afferent vessels, compared with the right hepatic lobe vessels, favors relatively less attenuation of caudate lobe vasculature by adjacent hepatic fibrosis. The resulting discrepancy between perfusion of the caudate lobe and right hepatic lobe may be responsible for the caudate lobe enlargement **,**

Our finding of significant association between the presence of portosystemic collaterals and esophageal varices agree with **Caletti et al. (15)** who reported the prognostic value of portosystemic collaterals in patients with esophageal varices.

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Regarding the role of right lobe diameter of the liver /serum albumin as a non-invasive, inexpensive and simple predictor of OVS, we found that there was a statistically significant difference between Patients with OVs and without OVS as regards the right lobe diameter of the liver /serum albumin. We also found a cut off value >2.80 could significantly predict OVS with sensitivity 80.9%, specificity 53.6% PPV 74.5%, and NPV 62.5%. These results are congruent with those of **Alempijevi** *et al. (5)* who found that the grades of varices tend to increase as the right liver lobe/ albumin ratio increases. Considering the right liver lobe/albumin ratio cut-off value of 4.42, this had a sensitivity of 83.3% and specificity of 29.5% for patients with varices requiring prophylactic endoscopic management.

On the other hand, **El Ray** *et al.* **(16)** found that right liver lobe diameter/ serum albumin had no role in prediction of OVS presence.

NIHCED score was originally developed by **Obrador et al. (17)** in order to   discriminate between cirrhotic and non-cirrhotic chronic hepatitis C patients. They reported that at a cut off >22, this index has a sensitivity of 80%, specificity of 96% and diagnostic accuracy of 94%**.** We have demonstrated the ability of the NIHCED score to distinguish between advanced fibrosis and absence of fibrosis or portal expansion (cut off score>45).We found a sensitivity of 70.2%, specificity of 78.6%, PPV of 84.6%, NPV of 61.1%, and diagnostic accuracy of 74.4% with an AUC of 0.77(95% CI: 0.66-0.86).

Bejarano et al. **(8**) reported the ability of the NIHCED score to distinguish between advanced fibrosis and absence of fibrosis or portal expansion (cut off score > 6) has a sensitivity of 72%, specificity of 76.3%, PPV of 81%,

NPV of 63.7%, and diagnostic accuracy of 72.5%.

Vergara et al. (18) tested the ability of NIHCED score to predict the development of liver cirrhosis in patients with chronic hepatitis C during follow up (4-10years). They reported that the AUC for development of cirrhosis during follow up was 0.79.

In conclusion, the NIHCED score is as effective as other non-invasive indices for determining the presence of varices. The addition of echographic data introduces prognostic factors into the information obtained NIHCED score is simple and easy to apply in any outpatient clinics. Future studies are needed to evaluate the utility of these non-invasive methods for the long-term follow-up of patients with liver cirrhosis

References
(1)Schaffner   H,   Popper   (1963): Capillarization   of   the   sinusoids. Gastroenterology 44:339–42.

(2)   Garcia-Tsao G, Groszmann RJ, Fisher RL, et al. (1975): Portal pressure, presence of gastroesophageal varices and variceal bleeding. Hepatology 5:419-24.

(3)   Naeije R (2003). Single beat estimation of right ventricular end systolic pressure volume relationship. Am J Physiol Circ Physiol 284:1625-30.

(4) Sarwar S, Khan AA, Alam A, et al. (2004):   Non-endoscopic   prediction   of esophageal varices in cirrhosis. J Coll physicians Surg Pak 15(9):528-31.

5) Alempijevic T, Bulat V, Djuranovic S, et al. (2007): Right liver lobe/albumin ratio: contribution   to   non-invasive assessment of portal hypertension. World J. Gastroenterol 13: 5331–5.

(6) Bejarano G, Vergara M, Gil M, et al. (2009): Prospective evaluation of liver fibrosis in chronic viral hepatitis C infection using the Sabadell NIHCED (non-invasive hepatitis C related cirrhosis early detection) index. REV ESP ENFERM DIG 5 : 325-35.

(7) Huber A, Ebner L, Heverhagen J, et al. (2015): State-of-the-art imaging of liver   fibrosis   and   cirrhosis: A

comprehensive review of current applications and future perspectives. European journal of radiology open 2: 90-100.

(8) De Franchis and Primignani M (2001): Natural history of portal hypertension with cirrhosis. Clin Liver Dis 5: 645-63

(9)Peck-Radosavljevic M (2000): Thrombocytopenia in liver disease. Can J Gastroenterol. 14(Suppl D):60D–6D

(10) Domenicali M, Baldassarre M, Giannone FA, et al. (2014): Posttranscriptional changes of serum albumin: clinical and prognostic significance in hospitalized patients with cirrhosis. Hepatology 60:1851–60

(11)Mandal L, Mandal SK, Bandyopadhyay D et al. (2001): Correlation of portal vein diameter and splenic size with gastroesophageal varices in cirrhosis of liver. J Ind Aca Clin Med 12(4):266-70

(12) Farooqi JI, Ahmed H, Ikramullah Q, et al. (2007): Predictors of esophageal varices in patients of liver cirrhosis. JPMI 21(1):60-64.

(13) Dumont AE, Amorosi E, Stahl WM (1970): Significance of splenomegaly in patients with hepatic cirrhosis and bleeding esophageal varices. Ann Surg 171:522-6.

(14) Dib N, Konate A, Oberti F, et al. (2005): Non-invasive diagnosis of portal hypertension in cirrhosis. Application to the primary prevention of varices. Gastroenterol Clin Biol 29(10):975-87.

(15) Caletti GC, Bolondi L, Arienti V, et al. (1983): Assessment of gastroesophageal collateral veins in portal hypertension by means of endoscopic ultrasonography Gut 24: 45

(16) El ray A, Azzab M, Mohamed I, et al. (2015): Non-invasive predictors for the presence, grade and risk of bleeding from esophageal varices in patients with post hepatitic cirrhosis. J. Egypt. Soc. Parasitol 45: 421–8.

(17) Obrador BD, Prades MG, Gómez MV, et al. (2006): A predictive index for the diagnosis of cirrhosis in hepatitis C based on clinical, laboratory, and ultrasound findings. Eur J Gastroenterol Hepatol 18: 57-62

(18) Vergara M, Gil M, Dalmau B, et al. (2008): Historia natural del carcinoma hepatocelular en una cohorte de pacientes de un hospital comarcal. Rev Esp Enferm Dig 100: 682-7