

Evaluation of the Sabadell noninvasive hepatitis C-related cirrhosis early detection index and right lobe diameter to albumin ratio in the prediction of presence of varices in Egyptian cirrhotic patients

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Introduction

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 is esophagogastroduodenoscopy, but identification of noninvasive predictors of esophageal varices (OVs) will allow upper gastrointestinal tract endoscopy to be carried out only in a selected group of patients. Different noninvasive parameters including clinical, laboratory, and sonographic predictors are an alternative approach to perform selective screening endoscopy only in patients at high risk.

Objective

Our objective is to evaluate whether the noninvasive hepatitis C-related cirrhosis early detection (NIHCED) score and the right lobe diameter to albumin ratio can predict the presence of OVs in a group of Egyptian cirrhotic patients.

Patients and methods

Seventy-five patients with liver cirrhosis were enrolled in the study depending on the clinical evidence of stigmata of chronic liver disease (e.g. jaundice, ascites, palmar erythema, spider naevi, etc.) and ultrasonographic features of liver cirrhosis (e.g. coarse echo texture, shrunken liver, etc.).

Results

According to the esophagogastroduodenoscopy results, the patients were categorized into two groups: those with OVs (47 patients, 63%) and those without OVs (28 patients, 37%).

Receiver operating characteristic curve analysis of the NIHCED score was applied to both groups with a cutoff score of more than 45. The estimation cohort study had a sensitivity of 70%, specificity of 78%, and diagnostic accuracy of 74% with an area under the receiver operating characteristic curve of 0.77 (95% confidence interval, 0.66–0.86).

Receiver operating characteristic curve analysis of the right lobe diameter to albumin ratio was applied to both groups with a cutoff score of more than 2.80. The estimation cohort study had a sensitivity of 80%, specificity of 53%, and diagnostic accuracy of 67% with an area under the receiver operating characteristic curve of 0.67 (95% confidence interval, 0.55–0.77).

Conclusion

The NIHCED score and right lobe diameter to albumin ratio are simple noninvasive predictors of the presence of varices in Egyptian patients with liver cirrhosis.

Keywords:

hepatitis C virus liver disease, liver cirrhosis, noninvasive hepatitis C-related cirrhosis early detection index, predictive index

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Introduction

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 hepatic-portal venous pressure gradient exceeding 5

mmHg. Cirrhosis is the most common cause of portal hypertension in the western world [2].

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Portal hypertension results in the development of esophagogastric varices which often bleed. It also plays a role in the development of ascites, hepatorenal syndrome, and hepatic encephalopathy. Portal hypertension and the resulting portosystemic collaterals may also be responsible for the cardiopulmonary complications such as portopulmonary hypertension and hepatopulmonary syndrome [3].

Identification of noninvasive predictors of esophageal varices (OVs) will allow upper gastrointestinal tract (GIT) endoscopy to be carried out only in a selected group of patients, thus avoiding unnecessary intervention and at the same time not to miss patients at risk of bleeding [4].

To date, several predictive markers of the presence of varices in patients with liver cirrhosis including clinical, laboratory, and hepatic echographic data have been published.

The right liver lobe diameter/albumin was evaluated as a noninvasive parameter to determine the presence of OVs in patients with liver cirrhosis [5].

The Sabadell noninvasive hepatitis C-related cirrhosis early detection (NIHCED) index was originally designed to evaluate the presence of advanced fibrosis in patients with liver cirrhosis [6].

To the best of our knowledge, this index has not been previously evaluated in Egyptian cirrhotic patients.

Therefore, we conducted this study aiming to evaluate the diagnostic performance of the right liver lobe diameter/albumin and the Sabadell NIHCED index in the prediction of the presence of varices.

Patients and methods

Between October 2016 and September 2017, 75 patients were prospectively and consecutively recruited for the study. All patients were admitted to the Tropical Medicine and Gastroenterology Department, Sohag University Hospital.

Inclusion criteria

Patients with liver cirrhosis (clinically and sonographically proven) with no history of upper gastrointestinal bleeding.

Exclusion criteria

(1) Patients known to have OVs.

- (2) Patients who refuse endoscopic examinations to evaluate the presence and degree of OVs.
(3) History of previous upper gastrointestinal bleeding.

Ethical consideration

We got approval of Sohag Faculty of Medicine Ethics 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 the following:

- (1) Complete history taking and physical examination.
- (2) Laboratory investigations: aspartate aminotransferase, alanine aminotransferase, serum alkaline phosphatase, serum albumin, prothrombin time and concentration, total and differential bilirubin, hepatitis markers for HBV and HCV, blood sugar, hemoglobin level, and serum creatinine.
- (3) Assessment of the severity of liver disease.
- (4) Using the Child–Pugh score [7]: 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.
- (5) Abdominal ultrasonography.
 - (a) To evaluate liver size, the right lobe diameter in the medioclavicular line, caudate lobe diameter, echogenicity and any focal lesion, portal vein diameter, spleen, portosystemic collaterals, and detection of ascites.
 - (b) Right lobe diameter (right hepatic lobe atrophy is considered if longitudinal diameter <9 cm).
 - (c) Caudate lobe diameter (hypertrophy of the caudate lobe is considered if diameter >4 cm).

Calculation of the Sabadell NIHCED index [6]:

Variables	Point score
Age ≥ 60	13 points
Prothrombin time ≥ 1.1	10 points
Platelets $\leq 100\ 000$	15 points
Aspartate aminotransferase/Alanine aminotransferase ≥ 1	10 points
Caudate lobe hypertrophy	6 points
Right hepatic lobe atrophy	15 points
Splenomegaly	7 points

Upper gastrointestinal tract endoscopy

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

Statistical analysis

Quantitative data were represented as mean, SD, median, and range. Data were analyzed using Student's *t* test to compare the means of two groups. When the data were not normally distributed Mann-Whitney test was used to compare two groups. Qualitative data were presented as number and percentage and compared using either χ^2 test or Fisher's exact test. Graphs were produced by using Excel or STATA program (StataCorp LLC., Texas, USA). Data were analyzed by sensitivity, specificity, positive, and negative predictive value derived from the receiver operating characteristic curve. The diagnostic accuracy of different prognostic scores were expressed as the area under the receiver operating characteristic curve. 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

The study included 51 men and 24 women. The mean age of all patients was 53.11 ± 9.89 .

Among the 75 cirrhotic patients, 47 (63%) patients had OV's diagnosed by upper GIT endoscopy (Fig. 1).

Laboratory data of the studied population are summarized in Table 1.

Sonographic data of the studied population are summarized in Table 2.

All 75 patients were categorized into two groups according to the findings in the esophagogastroduodenoscopy: group A those without OV's (37%) and group B those with OV's (63%).

Splenomegaly, caudate lobe hypertrophy, right hepatic lobe atrophy, collaterals, and dilated splenic vein were significantly more common in patients with OV's ($P=0.01$, $P=0.003$, $P \leq 0.000$, $P=0.02$, $P=0.04$), respectively, as shown in Table 3.

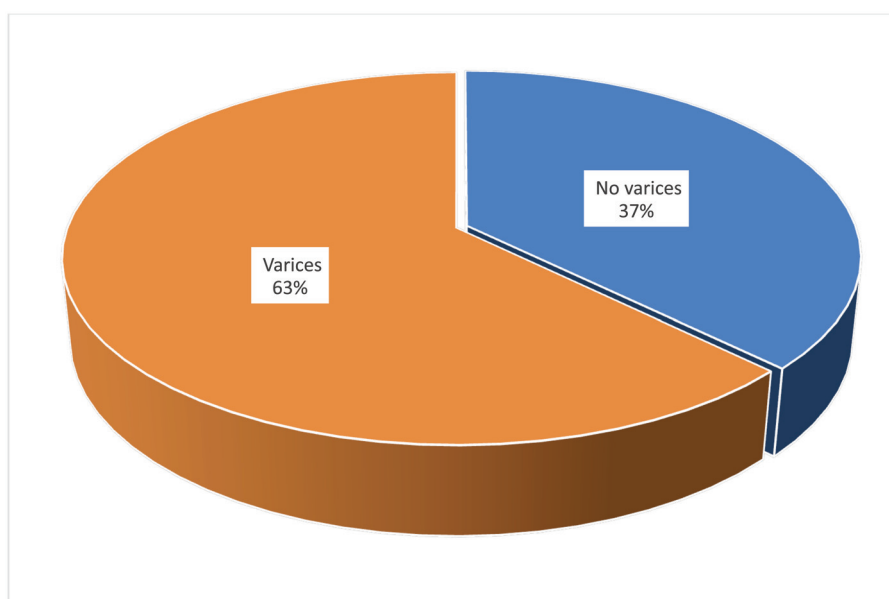
Patients with OV's had significantly lower value of platelet and albumin than those without OV's (Figs 2–4 and Tables 4 and 5).

There was a significant association between right lobe diameter to albumin ratio and presence of varices as shown in Table 6 and Fig. 5.

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 [8].

Figure 1



Prevalence of esophageal varices among studied population.

Table 1 Laboratory characteristics of studied population

Characteristics	All patients' summary statics (N=75)	Group A (N=28)	Group B (N=47)	P value
RBCs ($\times 10^{-6}/\mu\text{l}$)	3.92 \pm 1.21	3.78 \pm 1.19	4.01 \pm 1.23	0.42
WBCs ($\times 10^3/\mu\text{l}$)	7.13 \pm 3.74	7.57 \pm 4.47	6.87 \pm 3.26	0.82
Platelets ($\times 10^3/\mu\text{l}$)	102.69 \pm 44.98	123.96 \pm 52.28	90.02 \pm 34.80	0.001
ALT (IU/dl)	58.12 \pm 56.05	75.79 \pm 80.28	47.60 \pm 31.12	0.26
AST (IU/dl)	73.19 \pm 55.17	83.89 \pm 77.04	66.81 \pm 36.09	0.71
Total bilirubin (mg/dl)	2.02 \pm 2.30	2.43 \pm 3.05	1.77 \pm 1.70	0.81
Direct bilirubin (mg/dl)	0.90 \pm 1.45	1.1 \pm 1.74	0.78 \pm 1.25	0.70
Albumin (g/dl)	3.10 \pm 0.90	3.50 \pm 0.98	2.87 \pm 0.75	0.007
PT (s)	15.08 \pm 3.73	15.5 \pm 3.85	14.83 \pm 3.67	0.46
PC (%)	66.53 \pm 19.01	65.18 \pm 19.73	67.34 \pm 18.73	0.64

Data are expressed as mean \pm SD. ALT, alanine aminotransferase; AST, aspartate aminotransferase; PC, prothrombin concentration; PT, prothrombin time; RBC, red blood cells; WBC, white blood cells. Bold values mean significant relation p-value <0.05.

Portal hypertension commonly accompanies liver cirrhosis with the development of OV's and portal hypertensive gastropathy as major complications [9].

In Egypt, variceal causes of upper GIT bleeding are the most common, representing 70.1% of patients who are presenting with acute upper GIT bleeding. OV's alone represented 17.8% of causes of variceal bleeding, while combined esophageal and gastric varices represented 39.5% and isolated gastric varices 12.8% [10].

In this study, we evaluated the role of NIHCED score and right lobe diameter to albumin ratio in predicting the presence and grade of OV's 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 OV's 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 thrombopoietin either due to impaired production or rapid degradation may also add to thrombocytopenia.

Table 2 Ultrasonographic characteristics of studied population

Characteristics	All patients' summary statics (N=75)
Right lobe diameter (cm)	
Mean \pm SD	10.31 \pm 2.02
Median (range)	10 (7–17)
Right lobe atrophy [n (%)]	30 (40)
Caudate lobe diameter (cm)	
Mean \pm SD	4.04 \pm 0.98
Median (range)	4 (2–6)
Caudate lobe hypertrophy [n (%)]	27 (36)
PV diameter (mm)	
Mean \pm SD	11.65 \pm 2.83
Median (range)	11 (7–18)
Splenic vein [n (%)]	
Not dilated	68 (90.67)
Dilated	7 (9.33)
Ascites (by US) [n (%)]	
No	50 (66.67)
Yes	25 (33.33)
Splenomegaly (by US) [n (%)]	
No	20 (26.7)
Yes	55 (73.3)
Collaterals [n (%)]	
No	67 (89.33)
Yes	8 (10.67)

US, ultrasound.

The pathogenesis of low albumin level in patients with OV's is that synthesis is decreased because of the loss of hepatic cell mass. Also, the portal blood flow is often decreased and poorly distributed, leading to misdistribution of nutrients and oxygen. The flow of the substrate may affect certain functions of the liver, including protein synthesis [11].

Our results agree with Mandal *et al.* [12] who reported that platelet count and albumin are reliable predictors of variceal hemorrhage. These findings are in accordance with those of Farooqi *et al.* [13] who found that a platelet count of less than $65 \times 10^3/\mu\text{l}$ and serum albumin less than 2.2 g/dl are independent predictors of OV's on endoscopy.

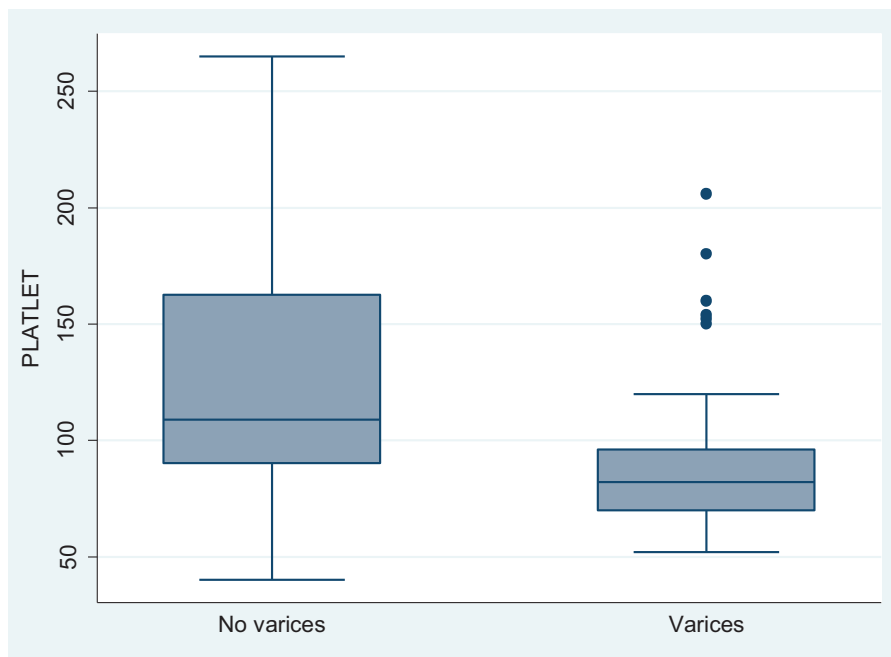
We found that splenomegaly was significantly associated with the presence of OV's in cirrhotic patients. The pathogenesis of splenomegaly in patients with OV's is that splenomegaly is not only caused by portal congestion, but it is mainly due to tissue hyperplasia and fibrosis. The increase in spleen size is followed by an increase in splenic blood flow, which participates in portal hypertension [14].

This finding correlates with the study carried out by Dib *et al.* [15] who reported that spleen length is an independent predictor of OV's.

Table 3 Comparison between patients without and with varices as regards sonographic findings

Characteristics	Group A with no varices (N=28)	Group B with varices (N=47)	P value
Right 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 [n (%)]			
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 [n (%)]			
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)	

US, ultrasound. Bold values mean significant relation p-value <0.05.

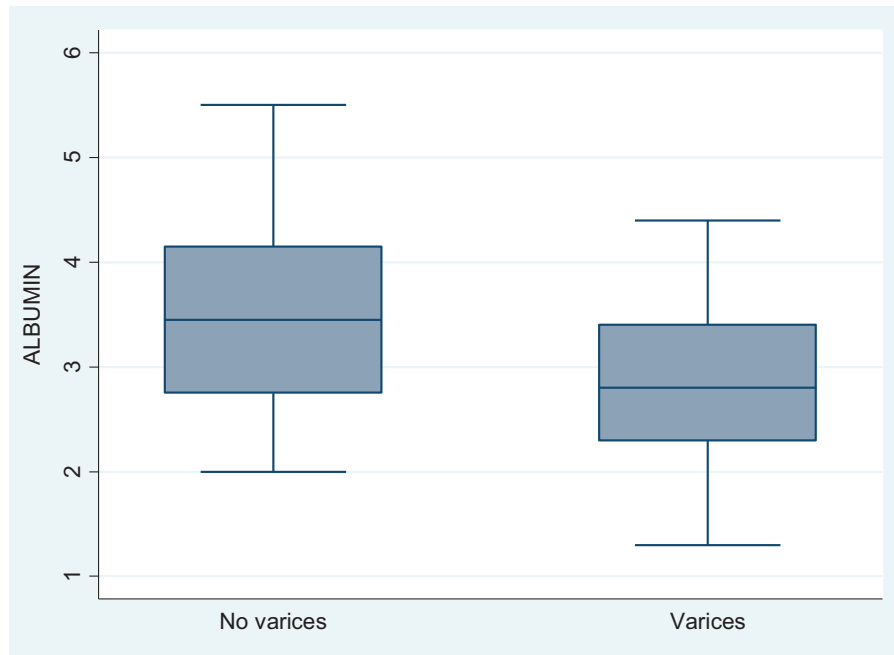
Figure 2

Comparison between patients without and with varices as regards platelets.

In the current study we found that ultrasonographic findings such as caudate lobe hypertrophy and collaterals were significantly associated with OVs.

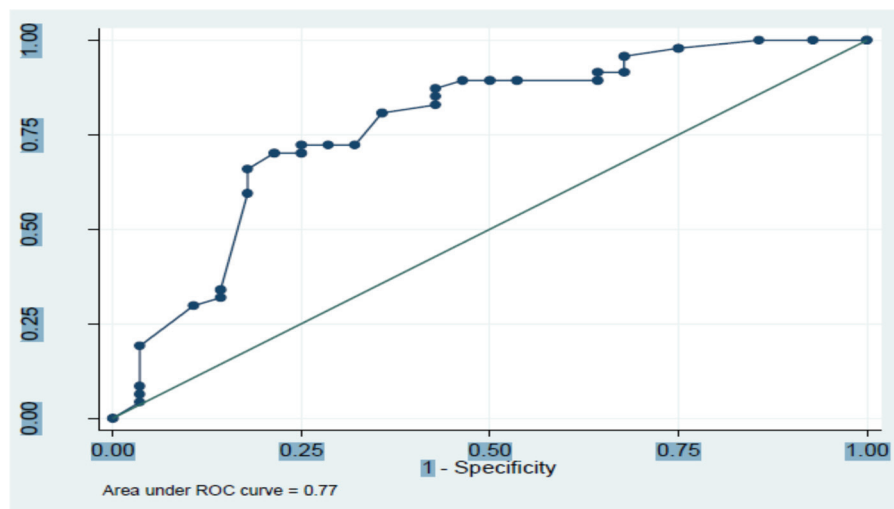
The pathogenesis of caudate lobe hypertrophy in patients with OVs is that the caudate lobe is anatomically distinct from the left and right lobes as

Figure 3



Comparison between patients without and with varices as regards albumin.

Figure 4



ROC curve analysis of NIHCED score in predicting varices. NIHCED, noninvasive hepatitis C-related cirrhosis early detection; ROC, receiver operating characteristic.

it has its own portal veins, hepatic arteries, and 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 caudate lobe enlargement [16].

Our finding of significant association between the presence of portosystemic collaterals and OVs agree

with Caletti *et al.* [17] who reported the prognostic value of portosystemic collaterals in patients with OVs.

Regarding the role of right lobe diameter of the liver/serum albumin as a noninvasive, inexpensive, and simple predictor of OVs, we found that there was a statistically significant difference between patients with OVs and those without OVs. We also found that a cutoff value more than 2.80 could significantly predict OVs with a sensitivity of 80.9%, specificity of 53.6%, positive predictive value of 74.5%, and negative

Table 4 Summarizes the laboratory and echographic data included in the noninvasive hepatitis C-related cirrhosis early detection score

Variables	Group A (N=28)	Group B (N=47)	P value
Age \geq 60			
No	19 (67.86)	34 (72.34)	0.68
Yes	9 (32.14)	13 (27.66)	
Prothrombin time \geq 1.1			
No	22 (78.57)	36 (76.60)	0.84
Yes	6 (21.43)	11 (23.40)	
Platelets \leq 100 000			
No	15 (53.57)	9 (19.15)	0.002
Yes	13 (46.43)	38 (80.85)	
AST/ALT \geq 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			
Mean \pm SD	30.21 \pm 20.53	49.43 \pm 16.34	0.0001
Median (range)	26.5 (0–76)	53 (10–76)	

ALT, alanine aminotransferase; AST, aspartate aminotransferase; NIHCED, noninvasive hepatitis C-related cirrhosis early detection. Bold values mean significant relation p-value <0.05.

Table 5 Area under the curve, sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of noninvasive hepatitis C-related cirrhosis early detection score ratio in predicting varices

Variable	Cut off point	AUC (95% CI)	Sensitivity	Specificity	PPV	NPV	Accuracy	P value
NIHCED score	>45	0.77 (0.66–0.86)	70.2	78.6	84.6	61.1	74.4	<0.00011

AUC, area under the receiver operating characteristic curve; CI, confidence interval; NIHCED, noninvasive hepatitis C-related cirrhosis early detection; NPV, negative predictive value; PPV, positive predictive value.

Table 6 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	NPV	Accuracy	P value
Right lobe D/albumin ratio	>2.80	0.67 (0.55–0.77)	80.9	53.6	74.5	62.5	67.3	0.01

AUC, area under the receiver operating characteristic curve; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.

predictive value of 62.5%. These results are congruent with those of Alempijevic *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 cutoff 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.* [18] found that right liver lobe diameter/serum albumin had no role in the prediction of OV's presence.

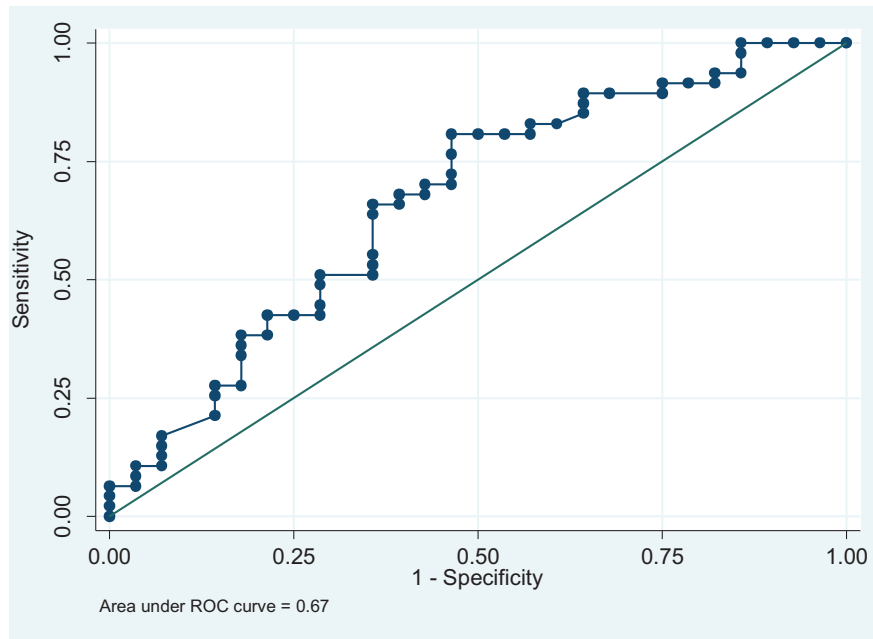
NIHCED index was originally developed by Obrador *et al.* [19] in order to discriminate between cirrhotic and noncirrhotic chronic hepatitis C patients. They

reported that at a cut off more than 22, this index has a sensitivity of 80%, specificity of 96%, and diagnostic accuracy of 94%.

Bejarano *et al.* [6] reported the ability of the NIHCED score to distinguish between advanced fibrosis and absence of fibrosis or portal expansion. At a cutoff score more than 6 it has a sensitivity of 72%, specificity of 76.3%, positive predictive value of 81%, negative predictive value of 63.7%, and diagnostic accuracy of 72.5%.

Vergara *et al.* [20] tested the ability of NIHCED score to predict the development of liver cirrhosis in patients

Figure 5



ROC curve analysis of right lobe diameter to albumin ratio in predicting varices. ROC, receiver operating characteristic.

with chronic hepatitis C during the follow-up (4–9, 10years). They reported that the area under the receiver operating characteristic curve for the development of cirrhosis during the follow-up was 0.79.

As regards the role of NIHCED score in predicting the presence of OVs in cirrhotic patients, to the best of our knowledge, our study is the first one that evaluate the role of the NIHCED in the prediction of OVs in cirrhotic patients. A combination of laboratory and hepatic echographic data is of value because in patients in whom laboratory parameters are within the normal range, the radiological data included in this index may be of greater value. Caudate lobe hypertrophy, splenomegaly, or right hepatic lobe atrophy would suggest, with a high degree of sensitivity and specificity, that a patient has advanced fibrosis.

In conclusion, both NIHCED score and right lobe/albumin ratio are as effective as other noninvasive indices for determining the presence of varices. The addition of hepatic echographic data introduces prognostic factors into the information obtained. NIHCED score is simple and easy to apply in any outpatient clinic.

Future studies are needed to evaluate the utility of these noninvasive methods for the long-term follow-up of patients with liver cirrhosis.

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Conflicts of interest

There are no conflicts of interest.

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