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USING THE NONINVASIVE FIBROSIS SCORES AS A PROGNOSTIC MARKER FOR VARICES NEEDING TREATMENT IN ADVANCED LIVER CIRRHOSIS

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ABSTRACT
The size and bleeding of noninvasive assessment of esophageal varices (EVs) may reduce endoscopic burden, cost and drawbacks. This study aimed to evaluate the diagnostic performance of noninvasive fibrosis scores (AAR, APRI, FIB-4, King and VITRO scores) to predict the presence of EVs and high-risk varices needing treatment (VNT) in HCV-related liver cirrhosis of Iraqi patients. This prospective study included assessing 120 HCV-related advanced compensated cirrhotic patients with no history of bleeding who underwent screening endoscopy for EVs. AAR, APRI, FIB-4, King and VITRO scores. Results of our study showed that esophageal varices were found in 94 patients (78.3%) and VNT in 73 patients (60.8%). Apart from AAR, all scores demonstrated statistically significant correlations with the presence and size of EVs. Noninvasive fibrosis scores can predict the presence of EVs and VNT. VITRO score was the best predictor with higher accuracy for clinical applicability than studied scores.

KEYWORDS: Esophageal Varices, Hepatitis C, Liver Cirrhosis, VITRO Scores.

INTRODUCTION
Esophageal varices (EVs) contribute to cirrhosis-related morbidity and mortality which are found in 60% - 80% of cirrhotic patients and correlated with the severity of liver disease.[1] [2] [3] Mortality from acute variceal bleeding is still very high, about 25% - 35%.[4] [5] Moreover, the mortality is up to 3.4 per year in patients with varices who have never bled and 57% per year in patients with variceal bleeding.[1] [6] Thus, endoscopic screening is recommended by all current guidelines at the time of the diagnosis of cirrhosis to identify those at risk of bleeding, e.g., large varices (which are found up to 30%), so that prophylactic therapy can be administered.[7] [8] In addition, it should be repeated every 2 - 3 years in patients who do not have varices and 1 - 2 years in those with small varices.[9] In order to avoid the endoscopic burden, cost, drawbacks, unpleasant and repeated examinations to the patients, several non-invasive parameters have been investigated for prediction of the presence and the size of EVs.[10] [11] [12] As it was postulated that the progressive fibrotic remodeling of the liver increases the resistance to hepatic sinusoidal blood flow and hence, it increases portal venous pressure causing esophageal and gastric varices.[3] In this study, we aimed to investigate the ability of five noninvasive fibrosis scores (AAR, APRI, FIB-4, King and VITRO scores) to predict the presence and the size of EVs in hepatitis C virus (HCV)-related cirrhosis of Iraqi patients in comparison to upper endoscopy.

MATERIALS AND METHODS
This prospective study was carried out at liver and digestive system hospital in Baghdad/Iraq from May 2016 to February 2017. The study protocol was approved by the local ethics committee of the liver and digestive system hospital and was in accordance with the previsions of the Declaration of Helsinki. Informed consent was obtained from all the participants before enrollment in the study.

This study included 120 adult patients with liver cirrhosis selected consecutively from inpatient wards of the liver and digestive system hospital. Cirrhotic patients had diagnostic criteria of liver cirrhosis (LC) by clinical, biochemical and ultrasonographic findings. The cause of liver dysfunction was hepatitis C. The severity of liver cirrhosis was assessed according to Child-Pugh classification.[13] Patients with decompensated cirrhosis (late Child B and Child C), active bleeding, previous endoscopic sclerosis or band ligation of EVs, previous transjugular intrahepatic portosystemic stent shunt or on

β-blocker therapy were excluded. Also, patients with severe cardiopulmonary, renal insufficiency, uncontrolled diabetes mellitus, active infections, HIV or HBV co-infections, malignancy, prior antiviral, immunosuppressive therapy, recent anticoagulant therapy, alcohol consumption or liver transplantation were excluded.

At the study entry, detailed clinical history and examination were taken and abdominal ultrasonography was undertaken. Blood samples were collected from stable patients for laboratory investigations including complete blood count, liver, kidney function tests and serum von-Willebrand factor Antigen (vWF-Ag) levels that were measured by using a fully automated STA analyser and vWF6 Liatest (Diagnostic Stargo, Paris, France) according to the instructions of the manufacturer.

Upper gastrointestinal endoscopy was done for evaluation of the presence, grade of EVs and stigmata of bleeding by an experienced endoscopist who was blinded to the outcomes of the study. Esophageal varices were graded as following: no varices, small varices without stigmata of bleeding and varices with stigmata of bleeding that need treatment that were large varices and small varices with red signs and known as high risk varices needing treatment (VNT).[6] [14]

Statistical Analysis

All statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS) for Windows version 18 (SPSS Inc., Chicago, IL, USA) and MedCalc program. The quantitative data were expressed as mean ± standard deviation (SD) and qualitative data were expressed as percentage. Spearman's rank correlation coefficient (r) was used to find correlations. Logistic regression analysis was used to establish the best model for prediction of high risk esophageal varices needing treatment. All tests were Two-tailed and statistical significance was assessed <0.05.

RESULTS

This study included 120 patients with HCV-related liver cirrhosis who underwent upper digestive endoscopy; 73 were Child-Pugh class A (60.8%), and 47 were early Child-Pugh class B (39.2%). Baseline demographic and clinical characteristics of the studied patients were summarized in table (1), where, 26 (21.7%) patients had no esophageal varices (EVs), 21 (17.5%) had varices without stigmata of bleeding and 73 (60.8%) patients had high risk varices needing treatment (VNT) that were large and small varices with red signs.

Table 1: Basal characteristics of study patients.

	Total (n = 154)
Age (years, mean ± SD)	51.4 ± 9.5 (41 - 80)
Sex	
Male	72 (60.0%)
Female	48 (40.0%)
Laboratory parameters (mean ± SD)	
S. bilirubin (mg/dl)	1.8 ± 0.7
S. albumin (g/dl)	3.1 ± 0.7
AST (IU L−1)	37.1 ± 11.2
ALT (IU L−1)	51.9 ± 16.9
INR	1.5 ± 0.3
Platelets (109 L−1)	81 ± 31
vWF-Ag%	121 ±28
Child-Pugh score (mean ± SD)	8 ± 3
Non-invasive scores (mean ± SD)	
AAR	0.79 ± 0.5
APRI	1.25 ± 0.51
FIB-4	3.9 ± 1.7
King	38 ± 18.4
VITRO	1.66 ± 0.61
Esophageal varices (%)	
No	26 (21.7%)
Small varices without red signs	21 (17.5%)
Small varices with red signs	24 (20.0%)
Large varices	49 (40.8%)
SD: standard deviation; AST: aspartate aminotransferase; ALT: alanine aminotransferase; INR: international normalized ratio; AAR: aspartate aminotransferase-alanine aminotransferase ratio; APRI: AST-platelet ratio index; FIB-4: fibrosis-4 index.	

Noninvasive fibrosis scores and esophageal varices

Apart from AAR, significant elevations in the mean values of noninvasive fibrosis scores (APRI, FIB-4, King and VITRO) were noted in patients with EVs compared to those without EVs (Table 2), and in patients with high risk VNT than patients without (Table 2). In addition, these scores (APRI, FIB-4, King and VITRO) were significantly correlated with the grades of esophageal varices, where, VITRO score had the strongest correlation (r = 0.718, P < 0.005). On the other hand, no significant correlation was found between ARR and variceal grades (r = 0.117, P = 0.232) (Table 3).

Table 2: Noninvasive fibrosis scores regarding the presence and size of esophageal varices.

	The presence of esophageal varices		
Noninvasive score	**Patients without EVs (n = 26)**	**Patients with EVs (n = 94)**	**P value**
AAR	0.64 ± 0.30	0.69 ± 0.40	0.554
FIB-4	0.69 ± 0.45	1.55 ± 0.62	<0.005
FIB-4	2.51 ± 1.29	4.35 ± 1.39	<0.005
King	23.31 ± 12.56	39.8 ± 17.8	<0.005
VITRO	0.91 ± 0.18	1.63 ± 0.78	<0.005
The size of esophageal varices			
	Patients with no or small EVs without red signs (n = 47)	**Patients with high risk EVNT (n = 73)**	**P value**
AAR	0.71 ± 0.24	0.79 ± 0.36	0.182
FIB-4	0.78 ± 0.37	1.38 ± 0.64	<0.005
FIB-4	2.50 ± 1.31	4.49 ± 1.51	<0.005
King	23.35 ± 11.60	43.61 ± 17.2	<0.005
VITRO	0.97 ± 0.18	1.99 ± 0.44	<0.005
P value < 0.05 = significant. EVs: esophageal varices; EVNT: esophageal varices needing treatment; AAR: aspartate aminotransferase-alanine aminotransferase ratio; APRI: AST-platelet ratio index; FIB-4: fibrosis-4 index.			

Table 3: Noninvasive fibrosis scores and size of esophageal varices.

	r	**P value**
AAR	0.117	0.232
FIB-4	0.531	<0.005
FIB-4	0.503	<0.005
King	0.521	<0.005
VITRO	0.718	<0.005
r: Spearman's rank correlation coefficient; P value < 0.05 = significant. AAR: aspartate aminotransferase-alanine aminotransferase ratio; APRI: AST-platelet ratio index; FIB-4: fibrosis-4 index.		

We tried to construct a model for predicting the development of EVs and VNT by binary logistic regression analysis (forward: LR) (Table 4). For predicting EVs, the presence or absence of varices was the dependent factor and APRI, FIB-4, King and VITRO scores were independent variables and the accuracy of this model was 70.4%. After removal of insignificant predictors (i.e., APRI and FIB-4), the accuracy of the model became 81.7%. If only VITRO was used, the accuracy of the model was 85% as shown in (Table 4). For prediction of VNT, dependent factors were either small or large varices while the independent factors were APRI, FIB-4 King and VITRO (significantly associated scores in univariate analysis). The accuracy of this model was about 60.1%. After removal of insignificant predictors (i.e., APRI, FIB-4 and King), the accuracy of the model becomes 83.2% where only VITRO was used (Table 4).

Table 4: Diagnostic models of esophageal varices and large esophageal varices.

	B	**S.E.**	**Wald**	**df**	**Sig.**	**Exp(B)**	**Accuracy**
Variables in the Equation (for prediction of esophageal varices)							
VITRO	6.709	1.466	18.96	1	<0.001	909.344	85.0%
Constant	−5.134	1.121	22.127	1	<0.001	0.007	
Variables in the Equation (for prediction of esophageal varices needing treatment)							
VITRO	3.651	0.531	41.348	1	<0.001	37.281	83.2%
Constant	−5.181	0.867	35.461	1	<0.001	0.007	

DISCUSSION

In this study, we tried to approve the Baveno VI recommendation for prediction of EVs and VNT in compensated HCV-related cirrhosis with non-invasive parameters nearly different from that used in Baveno VI. As in many areas, Transient Elastography was not easily applicable or available. So, simple and easily applicable noninvasive fibrosis tests were evaluated. Evaluation of hepatic fibrosis may provide information about the presence and severity of portal hypertension as increased hepatic vascular resistance in cirrhosis is influenced by the presence and the extent of fibrosis.[15] [16]

In this study, we demonstrated the ability of noninvasive markers of liver fibrosis to predict the presence of EVs and their size in Iraqi patients with liver cirrhosis and compare them with upper endoscopy. Evaluation of hepatic fibrosis may provide information about the presence and severity of portal hypertension as increased hepatic vascular resistance in cirrhosis is influenced by the presence and the extent of fibrosis.[15] [16]

Identification of patients with EVs especially high risk varices by regular screening is fundamental as they candidates for prophylactic therapy.[7] [8] The size of varices has been identified as the principal predictor for variceal bleeding which occurs in up to 30%, and is associated with significant morbidity and mortality.[17] [18] [19] Several non-invasive parameters had been introduced for variceal screening to minimize the usage of endoscopy.[10] [11] [12]

We demonstrated that all the studied models (AAR, APRI, FIB-4, King and VITRO scores) had a good performance for the diagnosis of EVs, where, VITRO score is currently the most accurate method for the detection of EVs in patients with LC. We showed a clear correlation between the variceal size and the VITRO score as well as the other noninvasive tests except AAR.

Previous studies investigating APRI as a predictor for EVs in LC patients showed that a low AUC in predicting EVs (0.62) and Large EVs (0.71).[20] [21]

In our study, the VITRO score was significantly higher in patients with EVs than those without. It showed the closest correlation with variceal size. Our results are supported by Hametner et al.[22], who clearly demonstrated that VITRO score had diagnostic and predictive value in patients with clinically significant portal hypertension (CSPH) assessed by hepatic venous pressure gradient (HVPG) independently of Child-Pugh score and also, it had an impressive correlation with EVs ($P < 0.004$).

The increased diagnostic accuracy of VITRO score for prediction of EVs and its size may be attributed to incorporation of independent predictors of portal hypertension; platelets and vWF-Ag.[24] [25] Several studies revealed that platelet count was an independent predictor for the presence of esophageal varices.[24] [26]. Thrombocytopenia may be partially caused by pooling and sequestration of platelets in an enlarged spleen due to portal hypertension and therefore, it is an indirect marker of portal hypertension.[24] vWF is a marker of endothelial dysfunction that is considered a major determinant of the increased vascular tone of cirrhotic livers and therefore of the development of portal hypertension.[25] Ferlitsch et al.[25], and La Mura et al.[27], declared that circulating levels of vWF had a significant direct correlation with HVPG.

Elevated vWF-Ag levels in liver cirrhosis are partly due to increased synthesis by increased shear stress or bacterial infection associated with endothelial cell damage or reduced clearance by increased activity of ADAMTS13 (vWF cleaving protease).[23] Thus, VITRO score is significantly superior to AAR, APRI, FIB-4, and King for predicting EVs and high risk VNT. One reason for this superior predictive ability of VITRO is the inclusion of platelets (unlike AAR) and vWF-Ag (unlike all the studied scores), which are well-known predictors of portal hypertension and EVs in cirrhosis as shown in previous studies.[24] [25] [26] [27] In addition, it is simply calculated and its items are easily obtained and measured.

The limitations of this work are a single-centre study and lack of comparison between noninvasive fibrosis scores and measurement of HVPG; an accurate measurement of portal hypertension, as measuring HVPG is not routinely available in our area. These findings are needed to be confirmed by further multicentre prospective studies to validate the usefulness of VITRO score in clinical practice.

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