Scientific Research Publishing

Open Journal of Gastroenterology, 2017, 7, 230-242
http://www.scirp.org/journal/ojgas
ISSN Online: 2163-9469
ISSN Print: 2163-9450

Noninvasive Fibrosis Scores as Prognostic Markers for Varices Needing Treatment in Advanced Compensated Liver Cirrhosis

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How to cite this paper: Hassan, E.A., Abd El-Rehim, A.S., Sayed, Z. A., Ashmawy, A.M., Kholef, E.F.M., Sabry, A. and Elsewify, W.A. (2017) Noninvasive Fibrosis Scores as Prognostic Markers for Varices Needing Treatment in Advanced Compensated Liver Cirrhosis. *Open Journal of Gastroenterology*, **7**, 230-242.
https://doi.org/10.4236/ojgas.2017.78025

Received: June 23, 2017
Accepted: August 28, 2017
Published: August 31, 2017

Abstract

Background/purpose: Noninvasive assessment of esophageal varices (EVs), their size and bleeding stigmata may reduce endoscopic burden, cost and drawbacks. We aimed to evaluate the diagnostic performance of noninvasive fibrosis scores (AAR, APRI, FIB-4, King and VITRO scores) in predicting the presence of EVs and high risk varices needing treatment (VNT) in HCV-related cirrhosis of Egyptian patients. **Methods:** This prospective study included 154 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 were assessed. **Results:** Esophageal varices were found in 120 patients (77.9%) and VNT in 92 patients (59.7%). Apart from AAR, all scores demonstrated statistically significant correlations with the presence and the size of EVs. Using area under receiver operating characteristic curve (AUC), these scores were good predictors for the presence of EVs and VNT, where VITRO score had the highest AUC (0.920 and 0.900) and accuracy (97.1% and 87%), sensitivity (75, 82.6%), specificity (100, 93.5%), PPV (100, 95%) and NPV (53.2, 78.4%) with cutoffs >1.3 and >1.8 respectively. **Conclusion:** 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 Score

1. 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 Egyptian patients in comparison to upper endoscopy.

2. Materials and Methods

2.1. Study Design

This prospective study was carried out at Al-Rajhi Liver Center, Assiut University Hospital, Assiut Egypt, from May 2016 to February 2017. The study protocol was approved by the local ethics committee of the Assiut University 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.

2.2. Patients

This study included 154 adult patients with liver cirrhosis selected consecutively from inpatient wards of the departments of Tropical Medicine and Gastroenterology and Internal medicine, Al-Rajhi Liver Center, Assiut University Hospital.

Cirrhotic patients had diagnostic criteria of liver cirrhosis (LC) by clinical, bi-

ochemical 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.

2.3. Methods

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 included 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.

By data collection, non-invasive fibrosis scores were calculated as following:

- AAR = AST (U/L)/ALT (U/L) [14].
- APRI = (AST (U/L)/upper limit of normal)/platelet (10^9/L) × 100 [15].
- FIB-4 = [age (years) × AST (U/L)]/[platelet (10^9/L) × ALT (U/L)$^{1/2}$] [16].
- King score = age (years) × AST (U/L) × INR/platelets (10^9/L) [17].
- VITRO = vWF-Ag/platelets (10^9/L) [18].

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] [19].

2.4. Statistical Analysis

All statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS) for Windows version 16 (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. The receiver operating characteristic curves (ROC) were plotted to measure and compare the performance of different noninvasive models for predicting EVs and VNT. Using ROC, The value with the best sensitivity and specificity was chosen as the best cutoff value, in addition, calculation of positive (PPV) and negative (NPV) predictive value, positive and negative likelihood ratio (+LR, −LR) for prediction or exclusion of varices. 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.

3. Results

3.1. Characteristics of the Studied Patients

This study included 154 patients with HCV-related liver cirrhosis who underwent upper digestive endoscopy; 94 were Child-Pugh class A (61%), and 60 were early Child-Pugh class B (40%). Baseline demographic and clinical characteristics of the studied patients were summarized in Table 1, where, 34 (22.1%) patients had no esophageal varices (EVs), 28 (18.2%) had varices without stigmata of bleeding and 92 (59.7%) patients had high risk varices needing treatment (VNT)

Table 1. Basal characteristics of study patients.

	Total (n = 154)
Age (years, mean ± SD)	50.5 ± 8.5 (40 - 80)
Sex	
Male	92 (59.7%)
Female	62 (40.3%)
Laboratory parameters (mean ± SD)	
S. bilirubin (mg/dl)	1.7 ± 0.6
S. albumin (g/dl)	3.2 ± 0.8
AST (IU L^{-1})	36.4 ± 10.7
ALT (IU L^{-1})	52.2 ± 17.1
INR	1.4 ± 0.2
Platelets (10^9 L^{-1})	83 ± 29
vWF-Ag%	123 ±27
Child-Pugh score (mean ± SD)	8 ± 3
Non-invasive scores (mean ± SD)	
AAR	0.76 ± 0.4
APRI	1.22 ± 0.54
FIB-4	3.8 ± 1.8
King	37 ± 18.5
VITRO	1.64 ± 0.62
Esophageal varices (%)	
No	34 (22.1%)
Small varices without red signs	28 (18.2%)
Small varices with red signs	30 (19.5%)
Large varices	62 (40.2%)

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.

that were large and small varices with red signs.

3.2. 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 = 0.730, P < 0.001). On the other hand, no significant correlation was found between ARR and variceal grades (r = 0.129, P = 0.112) (Table 3).

Table 2. Comparison between noninvasive fibrosis scores as regarding the presence and size of esophageal varices.

Noninvasive score	The presence of esophageal varices		
	Patients without EVs (n = 34)	Patients with EVs (n = 120)	P value
AAR	0.66 ± 0.27	0.79 ± 0.42	0.101
APRI	0.79 ± 0.35	1.35 ± 0.52	<0.001
FIB-4	2.48 ± 1.32	4.15 ± 1.69	<0.001
King	23.27 ± 12.6	40.8 ± 18.1	<0.001
VITRO	0.94 ± 0.2	1.83 ± 0.56	<0.001
	The size of esophageal varices		
	Patients with no or small EVs without red signs (n = 62)	Patients with high risk EVNT (n = 92)	P value
AAR	0.69 ± 0.26	0.80 ± 0.47	0.07
APRI	0.89 ± 0.38	1.45 ± 0.52	<0.001
FIB-4	2.76 ±1.39	4.47 ± 1.64	<0.001
King	26.5 ±13.1	43.9 ± 18.4	<0.001
VITRO	1.13 ± 0.33	1.98 ± 0.54	<0.001

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. Correlation between noninvasive fibrosis scores and the size of esophageal varices.

	r	P value
AAR	0.129	0.112
APRI	0.546	<0.001
FIB-4	0.511	<0.001
King	0.544	<0.001
VITRO	0.730	<0.001

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.

3.3. Diagnostic Performance of Noninvasive Models for Prediction of EVs and VNT

By applying ROC curves, the diagnostic accuracies of AAR, APRI, FIB-4, King and VITRO scores as noninvasive predictors of EVs and VNT were studied to determine which score would have the most clinical utility for prediction (Figure 1 and Table 4). For predicting EVs (Figure 1(a)), the AUC was greatest for VITRO score (0.920) followed by FIB-4 and King scores (0.800 for each) and APRI score (0.795). For predicting VNT (Figure 1(b)), VITRO had the greatest AUC (0.900), followed by FIB-4 score (0.808), APRI score (0.790) and King score (0.783) while the AAR score was <0.70.

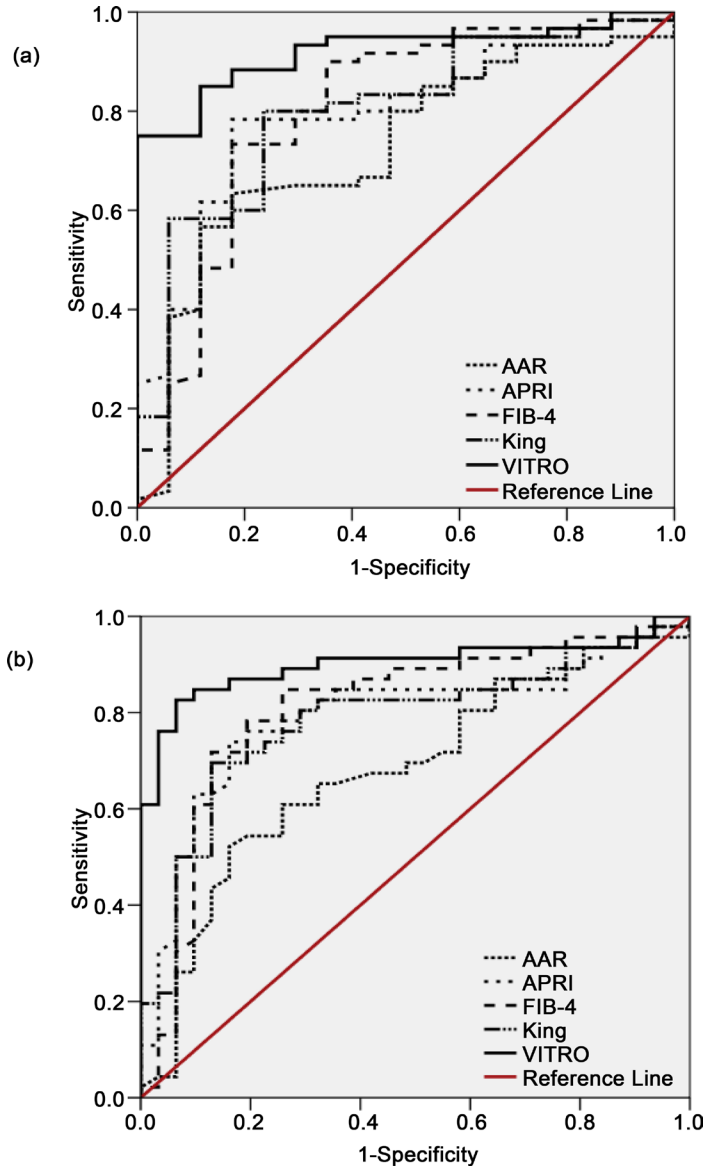

Figure 1. Area under the receiver operating characteristic curve (AUC) of noninvasive fibrosis scores to predict esophageal varices (a) and high risk esophageal varices (b). VITRO score had the highest AUC in predicting esophageal varices (AUC = 0.920) and high risk esophageal varices needing treatment (AUC = 0.900).

The optimum cutoff values of the previously mentioned scores to predict the presence of EVs and VNT were illustrated in Table 4 where; VITRO score had the highest diagnostic indices; with a cutoff value > 1.3, VITRO had 75% sensitivity, 100% specificity, 100% PPV, 53.2% NPV and 97.1% accuracy for the prediction of EVs and at a cutoff value > 1.8, VITRO had 82.6% sensitivity, 93.5% specificity, 95% PPV, 78.4% NPV and 87% accuracy for the prediction of VNT.

By using these scores, we tried to construct a model for predicting the development of EVs and VNT by binary logistic regression analysis (forward: LR) (Table 5). For predicting EVs, the presence or absence of varices was the dependant factor and APRI, FIB-4 King and VITRO scores (significantly associated scores in univariate analysis) were independent variables and the accuracy

Table 4. Diagnostic performance of noninvasive fibrosis scores for prediction of esophageal varices and large esophageal varices.

	Cut-off value	AUC 95% CI	SEN (%)	SPE (%)	PPV (%)	NPV (%)	+LR	−LR	Accuracy (%)
AAR for EV diagnosis	>0.67	0.726 (0.613 - 0.822)	63.3	82.4	92.7	38.9	3.59	0.45	67.5
AAR for EVNT diagnosis	>0.74	0.680 (0.563 - 0.781)	52.2	83.9	82.8	54.2	3.23	0.57	65
APRI for EV diagnosis	>0.85	0.795 (0.687 - 0.878)	78.3	82.4	94	51.9	4.44	0.26	79.2
APRI for EVNT diagnosis	>1.22	0.790 (0.682 - 0.874)	73.9	83.9	87.2	68.4	4.58	0.31	77.9
FIB-4 for EV diagnosis	>2.8	0.800 (0.694 - 0.883)	73.3	82.4	93.6	46.7	4.16	0.32	75.3
FIB-4 for EVNT diagnosis	>3.4	0.808 (0.702 - 0.889)	78.3	74.2	81.8	69.7	3.03	0.29	76.6
King for EV diagnosis	>24.74	0.800 (0.693 - 0.882)	80	76.5	92.3	52	3.4	0.26	79.2
King for EVNT diagnosis	>39.01	0.783 (0.674 - 0.869)	69.6	87.1	88.9	65.9	5.39	0.35	76.7
VITRO for EV diagnosis	>1.3	0.920 (0.835 - 0.969)	75	100	100	53.2	-	0.25	97.1
VITRO for EVNT diagnosis	>1.8	0.900 (0.811 - 0.957)	82.6	93.5	95	78.4	12.8	0.19	87

EV: esophageal varices; EVNT: esophageal varices needing treatment; AAR: aspartate aminotransferase-alanine aminotransferase ratio; APRI: AST-platelet ratio index; FIB-4: fibrosis-4 index; AUC: area under the curve; SEN: sensitivity; SPE: specificity; PPV: positive predictive value; NPV: negative predictive value; +LR: positive likelihood ratio; -LR: negative likelihood ratio.

Table 5. Diagnostic models of esophageal varices and large esophageal varices.

		B	S.E.	Wald	df	Sig.	Exp(B)	95% CI for EXP(B)		Percentage
								Lower	Upper	
Variables in the Equation (for prediction of esophageal varices)										
Step 1	VITRO	4.478	0.809	30.617	1	<0.001	88.026	18.022	429.952	87%
	Constant	−4.536	0.931	23.742	1	<0.001	0.011			
Step 2	King	−0.074	0.034	4.929	1	0.026	0.928	0.869	0.991	85.7%
	VITRO	6.811	1.556	19.161	1	<0.001	907.624	43.001	19,157.1	
	Constant	−5.120	1.103	21.557	1	<0.001	0.006			
Variables in the Equation (for prediction of esophageal varices needing treatment)										
Step 1	VITRO	3.645	0.555	43.101	1	<0.001	38.293	12.897	113.697	81.8%
	Constant	−5.165	0.845	37.362	1	<0.001	0.006			

of this model was 77.9%. After removal of insignificant predictors (*i.e.*, APRI and FIB-4), the accuracy of the model became 85.7%. If only VITRO was used, the accuracy of the model was 87% (odds ratio = 88.03, 95% CI = 18.02 - 430, P < 0.001) as shown in (Table 5).

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 59.7%. After removal of insignificant predictors (*i.e.*, APRI, FIB-4 and King), the accuracy of the model becomes 81.8% where only VITRO was used (odds ratio= 38.3, 95% CI = 12.9 - 113.7, P < 0.001) (Table 5).

4. 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 non invasive 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 [20] [21].

In this study, we demonstrated the ability of noninvasive markers of liver fibrosis to predict the presence of EVs and their size in Egyptian 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 [20] [21].

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 [22] [23] [24]. 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. In addition, VITRO score has the best performance for the diagnosis of high risk varices needing treatment.

In our work, AAR had the lowest performance in prediction of EVs (AUC = 0.726) and high risk EVs (AUC = 0.648), however these results were much better than that recorded by Deng *et al.* [24], who showed poor AUCs of AAR for EVs (0.596) and large EVs (0.601).

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) [25] [26]. Deng *et al.* [24], proposed that at a cutoff value of >0.87, the AUC was 0.539 for the diagnosis of any grade EVs with 68% sensitivity, 46.2% specificity, while at a cutoff value of >0.85, the AUC for predicting Large EVs was 0.506, 68.8% sensitivity, and 41.3% specificity. This study proposed a cutoff value of >0.85 for the diagnosis of EVs with AUC of 0.795. At this cutoff, the sensitivity was 78.3%, specificity was 82.4%, and the overall accuracy was 79.2%. Also, a cutoff of 1.22 for the diagnosis of high risk EVs was proposed at which AUC was 0.790, sensitivity was 73.9%, specificity was 83.9%, and the overall accuracy was 77.9%.

We used FIB-4 cutoff values > 2.8 and 3.4 for which AUCs were 0.8 and 0.808 for diagnosis of EVs and Large EVs with 73.3, 78.3% sensitivity and 82.4, 74.2% specificity respectively. Our findings were compatible with Hassan *et al.* [12], who reported Fib-4 having AUCs of 76 and 0.76 with 76, 72.9% sensitivity, 80, 66.7% specificity at cutoff > 2.8 and 3.3 for diagnosis of EVs and high risk EVs respectively. However, Fib-4 had been examined in other studies for the prediction of EVs and high risk EVs, having different AUCs and cutoff values; Sebastiani *et al.* [27], found that AUC was 0.64 for the prediction of EVs at a cutoff value of 3.5, while for the diagnosis of Large EVs, the AUC was 0.63 and the cutoff value was 4.3.

King score had been considered a satisfactory predictor of EVs. In the current study, at a cutoff value of 24.7, the score had an AUC of 0.800, 80% sensitivity, 76.5% specificity, 92.3% PPV, 52% NPV and 79.2% accuracy for the diagnosis of EVs. While for a cut-off value of 39.01, the AUC was 0.783, sensitivity was 69.6%, specificity was 87.1%, PPV was 88.9%, NPV was 65.9% and the accuracy was 76.7% for the prediction of VNT. In the retrospective study of Deng *et al.* [24], the best cutoff value for the diagnosis of EVs was 17.93, with an AUC of 0.639, 85.3% sensitivity, 44% specificity and 68.7% NPV, and the best cut-off value was 24.80 for diagnosis of high risk EVs, with an AUC of 0.645, 97% sensitivity, 53.6% specificity and 69.8% NPV.

In our study, the VITRO score was significantly higher in patients with EVs than those without. The diagnostic accuracy of VITRO for detecting EVs was significantly better than the other studied tests with an AUC of 0.920 (95%CI 0.835 - 0.969) with 75% sensitivity, 100% specificity, 100% PPV, 53.2% NPV and the highest accuracy (97.1%) at a cut-off > 1.3. It showed the closest correlation with variceal size, and at cut-off > 1.8 it had AUC, 0.9 (95%CI 0.811 - 0.957), 82.6% sensitivity, 93.5% specificity, 95% PPV, 78.4% NPV and 87% accuracy in detecting Large EVs suggesting its usefulness in identifying patients with large varices who need endoscopy. Our results supported by Hametner *et al.* [28], 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 [29] [30]. Several studies revealed that platelet count was an independent predictor for the presence of esophageal varices [29] [31]. 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 [29]. 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 [30]. Ferlitsch *et al.* [30], and La Mura *et al.* [32], 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) [28]. 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 [29] [30] [31] [32]. 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.

5. Conclusion

In conclusion, VITRO score had the best diagnostic performance to predict varices in liver cirrhosis in comparison to the other studied models that may aid in further improvement of the quality of noninvasive screening of EVs and high risk VNT and in further reduction of endoscopic requirement. Hence, it could offer a useful strategy to stratify high-risk patients who would benefit by intensive screening, and to recommend the prophylactic treatment.

Acknowledgements

Authors declared that no financial support from any agency.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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