



ASSESSMENT OF DIFFERENT NON-INVASIVE SCORE MODALITIES IN PREDICTION OF ESOPHAGEAL VARICES IN PATIENTS WITH LIVER CIRRHOSIS

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ABSTRACT

Background: Varices are a serious consequence of portal hypertension, and variceal bleeding is a life-threatening complication occurring in up to 30% of patients with cirrhosis. Despite the great improvement in diagnosis and the available therapeutic modalities, mortality from acute variceal bleeding may still reach up to 20%. Therefore, our aim was to assess the role of non-invasive score modalities in the prediction of the presence of EVs & to predict EVs severity. **Methods:** This Comparative cross-sectional study was conducted on a cohort of 90 cirrhotic patients. All patients were subjected to investigations include complete blood count, liver and kidney function tests, bleeding profile, random blood sugar, and serum sodium. The following scores were estimated: Child-Pugh score, MELD -Na⁺ score, AAR, APRI, FIB-4, and King's score. Upper GI endoscopy was done for evaluation of presence or absence of EVs. **Results:** Our results revealed that Kings Score is the most sensitive and specific score in predicting the presence of EVs, followed by APRI score while AAR score has the least sensitivity and specificity. FIB-4 score is the most sensitive scoring system in predicting severe EVs, followed by APRI, Kings, and AAR scores. Regarding specificity, King's Score is the most specific one followed by FIB-4, APRI and AAR. **Conclusions:** King's score has the highest sensitivity and specificity in EVs prediction followed by APRI. Regarding severe EVs, FIB-4 score is the most sensitive scoring system in the prediction of severe EVs. However, King's score is the most specific one.

Keywords: Esophageal Varices, GIT Endoscopy, Cirrhosis, Non-Invasive modalities.

INTRODUCTION

Liver cirrhosis is one of the most common causes of death in the world. Natural history of liver cirrhosis is primarily divided into four stages. Stages I, II, III, and IV are characterized respectively by neither varices nor ascites, varices without ascites or bleeding, ascites with or without varices, and variceal bleeding with or without ascites^[1].

Portal hypertension is a clinical syndrome defined by portal venous pressure gradient exceeding 10mmHg. PH is caused by increased resistance, increased blood flow, or both in the portal circulation^[2].

An elevated pressure difference between systemic and portal circulation directly contributes to the development of varices^[3].

Upper gastrointestinal endoscopy is the golden diagnostic test of varices in liver cirrhosis. However, because of its invasiveness, most patients are reluctant to undergo this procedure. Numerous non-invasive markers of varices have been explored in patients with liver cirrhosis. However, they may be rarely used in clinical practices^[4].

The aim of our study is to: assess the role of non-invasive score modalities (AAR, APRI, FIB-4, and King's score) in the prediction of the presence of EVs and their severity.

MATERIALS AND METHODS

This Comparative cross-sectional study was carried out in the Department of Internal Medicine, Faculty of Medicine, Zagazig University Hospitals from August 2018 to

January 2019, according to STROBE guidelines.

Ninety cirrhotic patients, presented with upper GI bleeding for 1st time, were included. Patients were categorized into 60 patients (Group I) were found to have EVs by means of upper GI endoscopy and 30 patients (Group II) were proven not to have EVs by means of upper GI endoscopy. We excluded patients who were diagnosed with malignant tumors, patients who receive oral anticoagulants, or those who didn't undergo upper GI endoscopy.

Written Informed consent was taken from the patient to participate in the study.

Approval for performing the study was obtained from the Internal Medicine Department, Zagazig University Hospitals after taking Institutional Review Board (IRB) approval. The study was carried out according to the declaration of Helsinki guidelines.

All patients were subjected to full history, thorough clinical examination and routine laboratory investigations in addition to Upper GI endoscopy with evaluation of presence or absence of EVs.

Patients classified according to Child -Pugh score (CPS) classification ^[5], where each measure is scored 1-3, with 3 indicating most severe derangement.

The following scores assessed accordingly:

MELD score = $MELD + 1.32 \times (137 - Na) - [0.033 \times MELD \times (137 - Na)]$ ^[6].

APRI = $\{(AST \text{ in IU/L}) / (AST \text{ Upper Limit of Normal in IU/L})\} / (Platelets \text{ in } 10^9/L)$ ^[7].

FIB-4 = $(Age \times AST) / (Platelets \times \sqrt{ALT})$ ^[8].

AAR = AST/ALT ratio ^[9].

King's score = $Age \times AST \times INR / Platelets$ ^[10].

Statistical analysis

All data were collected, tabulated and statistically analyzed using SPSS 20.0 for windows (SPSS Inc., Chicago, IL, USA) & MedCalc 13 for Windows (MedCalc Software bvba, Ostend, Belgium). Continuous variables were expressed as the mean \pm SD, median and range according to the normality of data where normally distributed data were expressed as

mean \pm SD whereas none normally distributed data were expressed as median and (range). The categorical variables were expressed as a number (percentage). Continuous variables were checked for normality by using the Kolmogorov Smirnov test. All normally-distributed data were analyzed using Independent Student (t) test. Data found to be non-normally distributed were analyzed using the Mann-Whitney U (MW) test. One-Way ANOVA was used to compare normally distributed variables in three groups. Kruskal-Wallis H (KW) test was used to compare non-normally distributed variables in three groups. Post-hoc Fisher's Least Significant Difference test (LSD) tests were used according to the homogeneity of variances. Percent of categorical variables were compared using the Chi-square (χ^2) test. Pearson product-moment correlation coefficient was used to assess correlation between different score and study parameters if data is parametric while Spearman's rank correlation coefficient (Spearman's rho) was calculated to assess the correlation between various study parameters. (+) sign as an indication for direct correlation i.e. increase frequency of independent lead to increase the frequency of dependent and (-) sign as an indication for inverse correlation i.e. increase the frequency of independent lead to decrease frequency of dependent, also we consider values near to 1 as strong correlation and values near 0 as weak correlation. Receiver operating characteristic (ROC) curve analysis was used to identify optimal cut-off values of the different scoring system for prediction of esophageal varices in patients with liver cirrhosis. All statistical comparisons were two-tailed with significance Level of P-value ≤ 0.05 indicates significant, p < 0.001 indicates highly significant difference while, P > 0.05 indicates Non-significant difference.

RESULTS

A highly significant difference was found between the studied groups in most of the studied demographic and clinical parameters table (1).

In group I all patients had esophageal varices (EVs) where 28.3% had mild EVs, 26.7% had moderate EVs and 45% had severe EVs, while no patient of group II had EVs. Also, in group I, 11.7% of patients had fundal varices while no patient of group II had fundal varices.

There were statistically significant differences between the two groups regarding spleen diameter as well as portal vein diameter however; there weren't statistically significant differences between patients with mild or moderate EVs and those with severe EVs

regarding spleen diameter as well as portal vein diameter.

While comparing different scoring systems between studied groups, there were statistically significant differences between studied groups regarding their APRI, FIB-4 & king's scores. While there wasn't a significant difference between them regarding AAR score table (2).

Kings score at a cut off value of 12.11 is the most sensitive and specific score in predicting the presence of EVs, followed by APRI score at a cut off value of 0.485 while AAR score has the least sensitivity and specificity figure (1).

Figures

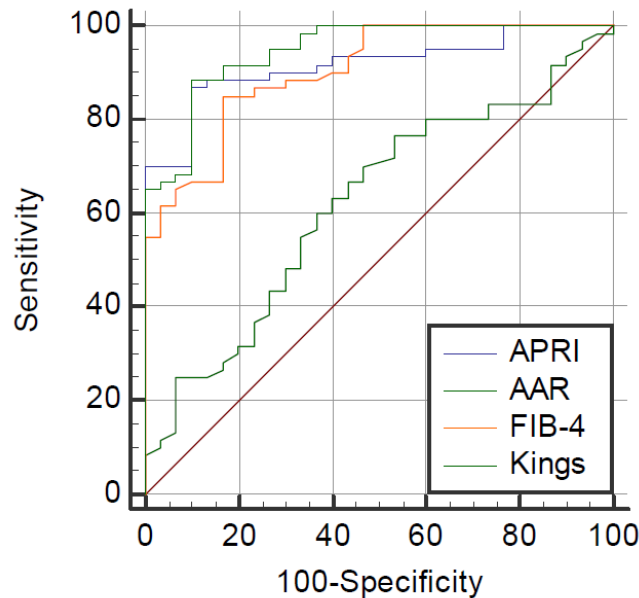


Figure 1 Comparison of ROC curve of role of different risk score in predicting EVs in patients with UGIB

Table 1 Demographic and clinical characteristics of the patients

Parameters	EVs patients(n=60)	Non EVs patients (n=30)	P
*Age (years)	53.48 ± 10.69	43.0 ± 16.98	.004
Males, n (%)	49 (81.7)	23 (76.7)	.78
Smoker, n (%)	33 (55)	19 (63.3)	.60
DM, n (%)	31 (51.7)	12 (40)	.41
HE, n (%)	27 (45)	---	<0.001
Ascites, n (%)	46 (76.7)	5 (16.7)	<0.001
[§] TLC ($\times 10^3/mm^3$)	5 (2.3 - 25)	7.3 (4 - 11)	<0.001
*Hemoglobin(g/dL)	9.42 ± 1.75	12.5 ± 1.65	<0.001
[§] Platelets($\times 10^3/mm^3$)	90 (33 - 192)	188 (120 - 455)	<0.001
*INR	1.53 ± .24	1.10 ± .15	<0.001
[§] Creatinine (mg/dL)	1 (.49 - 4.2)	.9 (.7 - 2.6)	.39
[§] Na(mEq/L)	131.8 (127-140)	140 (128 - 148)	<0.001
[§] ALT(U/L)	24 (8 - 76)	13.5 (4.6 - 38)	<0.001
[§] AST (U/L)	35 (10 - 76)	23 (12 - 44)	<0.001
[§] Albumin (g/dL)	2.6 (1.7 - 3.5)	4 (3 - 4.8)	<0.001
[§] T. bilirubin (mg/dL)	2.1 (.5 - 4.1)	1.1 (.4 - 2.3)	<0.001
[§] D. bilirubin (mg/dL)	1.5 (.22 - 3.1)	.7 (.06 - 1.8)	<0.001
[§] Spleen Diameter (cm)	16.5 (0 - 20)	12 (10 - 15)	<0.001
[§] PV Diameter (mm)	14 (9 - 16)	10 (8 - 14)	<0.001

*Data are presented as mean ± SD, while \$ data are presented in median (range).

Table 2 Scoring system between studied groups.

Parameters	EVs patients(n=60)	Non EVs patients (n=30)	P
APRI	1.25 (.19 - 3.21)	.29 (.08 - .88)	<0.001
AAR	1.45 (.63 - 3.5)	1.66 (1.1 - 3.04)	<0.001
FIB-4	4.76 (1.31 - 12.21)	1.03 (.29 - 4.27)	<0.001
King's score	35.87 (6.54 - 108.5)	4.11 (.78 - 30.8)	<0.001

Data are presented in median (range).

Table 3 Correlation coefficient between PV & Spleen diameters versus non-invasive scores

	PV diameter		Spleen diameter	
	<i>R</i>	<i>p</i>	<i>r</i>	<i>p</i>
<i>APRI</i>	.413	<0.001	.680	<0.001
<i>AAR</i>	-.05	.67	-.194	.07
<i>FIB-4</i>	.421	<0.001	.668	<0.001
<i>King's score</i>	.457	<0.001	.679	<0.001

DISCUSSION

Portal hypertension represents a pathologic increment in the portal venous pressure. Increased resistance to portal blood flow, the primary etiology in the portal hypertension pathophysiology, is in part due to morphological alternations occurring in long term liver diseases. This leads to the rerouting of blood flow away from the liver via collateral pathways to low-pressure systemic veins ^[11].

Variceal bleeding is one of the fatal portal hypertension-related complications in liver cirrhosis ^[12].

Severe bleeding from esophageal varices has been estimated to take place in about 30 - 40% of patients with cirrhosis ^[13] and carries significant morbidity and mortality ^[14]. Upper gastrointestinal endoscopy is the golden diagnostic method for varices. However, given the invasiveness and relatively high cost of endoscopy and poor patients' adherence, noninvasive diagnostic methods have been developed dramatically in the last decades ^[15].

In our study, there were significant differences between patients who had EVs and those hadn't, regarding spleen diameter as well as portal vein diameter, this constant with Mohanty et al ^[16] who found that portal vein diameter and splenic size were increased in patients with EVs than patients without EVs.

In contrast to Mohanty et al ^[16] who found a definite correlation between the increase in splenic size and portal vein diameter with the severity of EVs, our results showed no significant differences between patients with mild or moderate EVs and those with severe

EVs regarding spleen diameter as well as portal vein diameter.

However, our results constant with Jamil et al ^[17] whose results showed that portal vein diameter, estimated by trans abdominal ultrasound, is found to be an unsatisfactory noninvasive marker for predicting the esophageal varices (AUC=0.591;p=0.05). Moreover, many studies have shown similar results that ultrasound-dependent variables, such as vessel diameters and changes in waveforms, are poorly correlated with the presence of esophageal varices ^[18].

Our results showed that among patients who had EVs: 28.3% had mild EVs, 26.7% had moderate EVs and 45% had severe EVs. These results approximately similar to Zardi et al ^[19] who showed that among 195 Pakistani patients of hepatitis C positive chronic liver disease who had EVs: Grade 1 EVs presented in 79 (40.5%) of patients, Grade 2 presented in 44(21.9%) of patients, Grade 3 found in 62 (31.8%) and Grade 4 found in 10 (5.2%) patients.

In our study, there were significant differences between patients with EVs and those without as regard MELD & Child-Pugh scores. This in agreement with Peng et al ^[20], that conclude that both (Child-Pugh, and MELD) scores had significant prognostic value in the assessment of liver cirrhosis prognosis.

Also, our results showed significant differences between patients with mild or moderate EVs and those with severe EVs regarding their Child-Pugh score, however no significant difference between them regarding MELD score. This agrees with Cholongitas et al ^[21], who stated that MELD score does not

perform better than Child-Pugh score in non-transplant settings.

In our study, the diagnostic accuracies of APRI, AAR, FIB-4, King's as noninvasive predictors for EVs and for severe EVs requiring treatment were studied, by applying ROC curves, to determine which score would have the most clinical utility for prediction. For predicting EVs, the AUC was greatest for King's score (0.95) followed by APRI score (0.92), FIB-4 (0.90) and the lowest was AAR (0.62). For predicting severe EVs, the AUC was greatest for FIB-4 (0.93) followed by APRI score (0.87), King score (0.86) and the lowest was AAR (0.58). The results of Hassan et al^[22], who studied the diagnostic accuracies of the same scoring systems in predicting EVs among 154 patients with HCV-related liver cirrhosis, showed that the AUC for FIB-4 and King scores were (0.800 for each) followed by APRI score (0.795). The same study showed that FIB-4 score had the greatest AUC (0.808) in predicting severe EVs needing treatment, followed by APRI score (0.790) and King score (0.783) while the AAR score was <0.70.

Regarding APRI, our results show that APRI had high sensitivity and specificity in detecting severe EVs, this in agreement with Bao^[23] who stated that APRI positively correlated with the degree of EVs.

In our study, APRI at a cutoff of 0.485 was used to predict the existence of EVs and it was shown a sensitivity of 86.67%, a specificity of 90%, a PPV of 94.50% and a NPV of 77.1% while APRI at a cutoff of 1.104 was used to predict presence of severe EVs and it was shown a sensitivity of 85.2%, a specificity of 69.7%, a PPV of 69.7% and a NPV of 85.2%. In agreement with our results, Snyder et al^[24] had shown that APRI at a cutoff of 0.42 or less correctly detected mild fibrosis with a NPV of 95%. In addition, Lin et al^[25] stated that, for significant fibrosis, an APRI threshold of 0.7 was 77% sensitive and 72% specific & for severe fibrosis, a threshold of 1.0 was 61% sensitive and 64% specific. In the contrast, Zambam de Mattos et al^[26] that used APRI at a cutoff of 1.3, to predict the existence of EVs,

showed a sensitivity of 64.70%, a specificity of 72.70%, a PPV of 86.50% and a NPV of 43.20%.

Regarding AAR, in agreement with Kraja et al^[27] who stated that there was no evidence of any significant association between esophageal varices and AST/ALT ratio, our results revealed that there was no significant difference between patients with EVs and those without. This could be attributable to the affection of serum ALT levels by many factors, such as gender, body mass index, as well as hepatotoxic medications, which subsequently affect AAR results^[28].

As regard FIB-4, our results showed that FIB-4 has high sensitivity and specificity in detecting severe EVs, this in agreement with Bao^[23] who stated that FIB-4 positively correlated with the degree of EVs. On the same context, Vallet-Pichard et al^[29] stated that the FIB-4 index <1.45 had a NPV of 94.7% to exclude severe fibrosis with a sensitivity of 74 %.

In addition, FIB-4 index higher than 3.25 had a PPV, to confirm the existence of significant fibrosis, of 82.1% with a specificity of 98.2%. This agrees with our study results as Fib-4 at a cutoff of 2.1 was used to predict the existence of EVs and it was shown a sensitivity of 85%, a specificity of 83.3%, a PPV of 91% and a NPV of 73.5%. Similarly, Fib-4 at a cutoff of 4.25 was used to predict the presence of severe EVs with a sensitivity of 100%, a specificity of 78.79%, a PPV of 79.4% and a NPV of 100%.

As regard, King's score, in agreement with our results Cross et al^[30] showed that King's score had a good clinical utility in identifying patients with significant fibrosis and cirrhosis where it found that AUCs for detecting advanced fibrosis and cirrhosis of 0.82 and 0.89, respectively. Similarly, we found that King's score at cutoff value 12.11 could detect the presence of EVs with AUC of 0.95, a sensitivity of 88.33 % and specificity of 90 %. This in contrast to Kraja et al^[27] who stated that no evidence of any significant association between esophageal varices and King's score.

So, owing to the invasiveness of endoscopy, non-invasive scoring modalities should be used as screening tools prior to endoscopy being accurate and of low cost. More studies must be conducted to set down a reference cutoff value for APRI, FIB-4, and King's score for prediction of severe EVs.

CONCLUSION

Endoscopy is the golden method for EVs screening. However, non-invasive score modalities (APRI, FIB-4, and King's score) had a vital role in the prediction of the presence of EVs being cheap and applicable. King's score has the highest sensitivity and specificity in EVs prediction followed by APRI. AAR score was neither sensitive nor specific in predicting EVs; also, it had a negative correlation when correlated with spleen diameter & PV diameter.

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Limitations of the study:

Financial and technical obstacles limited usage of other non-invasive methods as esophageal Doppler, capsule endoscopy and liver elastography.

Conflict of Interest: Non declared.

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