Med. J. Cairo Univ., Vol. 91, No. 3, September: 1131-1139, 2023
www.medicaljournalofcairouniversity.net

Evaluation of the Novel PAP Score and Other Fibrosis Scores as Non-Invasive Alternative for Upper GI Endoscopy in Detection of Large Esophageal Varices in HCV-Induced Liver Cirrhosis

SHAIMAA M. ALI, M.D.*; FADY NASSIF, M.Sc.*; AHMED EL-MAZNY, M.D.*;
DINA ELGAYAR, M.D.** and REHAM ZEYADA, M.D.**

The Departments of Internal Medicine and Clinical and Chemical Pathology**, Kasr Al-Ainy Faculty of Medicine, Cairo University*

Abstract

Background: Hepatic cirrhosis patientsregularly undergo screening endoscopy forvarices. The availability of non-invasive tools for the screening of esophageal varices, their size and susceptibility for bleedingcan reduce the burden of unnecessary endoscopies, the cost and drawbacks.

Aim of Study: This work aimed to evaluate the diagnostic performance of a novel PAP score in detection of large-sized esophageal varices as well as other liver fibrosis scores namely Child-Pugh score, AAR, APRI, Fib-4 and Lok index.

Patients and Methods: This study included 90 HCV-induced cirrhotic patients aged ›21 years with no history of HCC, NSBB therapy or upper gastrointestinal bleeding. Patients were classified into 2 groups according to endoscopic size of varices: Group 1: 60 patients with large-sized esophageal varices i.e grade III-IV and group 2: 30 patients with small-medium sized esophageal varices i.e grade I-II. They were subjected to medical history interview, clinical examination, laboratory investigations and recent pelvi-abdominal ultrasound. Calculation of PAP, AAR, APRI, Fib-4, Child-Pugh and Lok scores and evaluation of their diagnostic performance in detection of large sized varices was done.

Results: PAP score had poor diagnostic performance in this study with an AUC of 0.559, p-value 0.406. On the other hand, AAR, APRI, FIB-4, Lok and Child-Pugh scores were capableof discriminating patients with large-sized varices (p<0.05). FIB-4 score had the best diagnostic accuracy at cut-off value of 4.7 with AUC of 0.951 and APRI score had a high diagnostic accuracy at a cut-off value of 1.45 with AUC of 0.947.

Conclusion: Non-invasive screening methods may have a value in detecting patients with large varices who need prophylactic treatment with beta-blockers. Findings of this study suggest the possible usage of FIB-4 and APRI as non-invasive tools to stratify cirrhotic patient into risk classes and possibly on the long run decrease the number of endoscopies required.

Key Words: *PAP score – Esophageal varices – Non-invasive screening – Liver fibrosis scores.*

Correspondence to: Dr. Shaimaa M. Ali,
The Department of Internal Medicine, Kasr Al-Ainy Faculty of Medicine, Cairo University

Introduction

CHRONIC hepatitis C virus infection (HCV) is a deleterious medical condition that impacts roughly 2% to 3% of the population worldwide. With approximately 14.7% of the population infected, Egypt has the highest prevalence of HCV in the world **[1]**. Cirrhosis is the final phase of chronic liver disease, which is made worse by portal hypertension **[2]**. Cirrhosis is the consequence of liver cells necrosis, followed by fibrosis and nodule formation. Hepatic architecture is disrupted which interferes with hepatic blood flow and function. This disruption leads to portal hypertension anddecreased hepatocellular function **[3]**. Globally, cirrhosis is major cause of hepatic-related death.

Portal hypertension is the pathologic increase in pressure in the veins that transport blood from the splanchnic organs to the liver. The increase in the pressure gradient between portal venous inflow to the liver and hepatic venous outflow (>5mmHg) leads to increase in portal pressure **[4]**. Pathology can be sinusoidal, presinusoidal or post sinusoidal. Sinusoidal causes are the most common and are mostly caused by liver cirrhosis **[5]**.

Varices is a consequence of portal hypertension andvariceal bleeding is one of the most serious life-threatening complications in cirrhosis and is the second most common decompensating event **[6]**.

The most frequent type is esophageal varices, which have a prevalence of 42.7% in Child-Pugh class A, around 70.7% in class B, and 75.5% in class C **[7]**. Gastric varices are present in 20% of the patients with portal hypertension **[8]** while ectopic varices cause up to 1-5% of all variceal bleeding **[9]**. According to research, the probability

of variceal bleeding, which is assumed to be 5-15 percent per year, is linked to variceal size [10]. The severity of liver failure (Child B/C) and/or the presence of red wale marks increase the risk. Despite advances in treatment, the total death rate from a variceal hemorrhagic event is still high, amounting to 15-25 percent at six weeks. It is even worse when variceal bleeding is combined with acute kidney injury and/or bacterial infections, where the risk of death rises markedly [11]. Moreover, rebleeding occurs in 60-70% of patients without secondary prophylaxis, frequently within one to two years of the bleeding episode [12]. These reasons highlight the need of screening cirrhotic patients for the presence of sizable varies that will warrant starting primary prophylaxis.

As per available surveillance tools for gastroesophageal varices,endoscopy is the gold standard procedure for diagnosis. It is usually recommended that at the time of cirrhosis diagnosis, a patient needs to undergo upper gastrointestinal endoscopy (GI) toidentify patients at riskof bleeding in order to start prophylactic treatment, either with endoscopic variceal ligation or beta blockers [13]. Even though, cirrhotic patients typically had clinically significant portal hypertension preceding development of esophageal varices (EV), and although varices are present in approximately 70% of Child-Pugh B or C patients, they are probably present in only 40% of Child-Pugh A patients. Given those figures, it is becoming increasingly evident that many patients with a recently diagnosed cirrhosis will undergo unnecessary endoscopy. And given the fact that, almosthalfthe patients diagnosed with liver cirrhosis may not develop EV up to 10 years after their initial diagnosis, the existing status places a considerable burden, not to mention expense on endoscopy units [14].

And therefore, there is an urgent need for a non-invasive method to screen patients for esophegeal varices and hence decrease the demand on endoscopies. Non-invasive methods include radiological methods like elastography and various laboratory methods. AST/ALT ratio (AAR), aspartate to platelet ratio index (APRI), FIB-4 index, Fibroindex, Forns Index, and LOK scoreare among some of the indices used to determine the extent of cirrhosis and discriminate esophageal varices sizes, with varying degrees of success.

Aim of this study was to assess a new test, PAP score, based on platelet count, alfa fetoprotein (AFP), and international normalized ratio (INR), as well as Child-Pugh score, AAR, APRI, Fib-4 and Lok index in the differentiation of variceal size.

Patients and Methods

Patients:

This comparative cross-sectional study included 90 HCV-induced cirrhotic patients with age ≥ 21 years of both sexes, with no history of HCC or upper GI bleeding. All subjects were recruited from Kasr Al-Ainy Hospital inpatients and outpatient clinics, over the period of eight months (from August 2020 to March 2021).

Inclusion criteria: HCV diagnosed by Anti-HCV antibody and PCR. Cirrhosis confirmed by pelviabdominal ultrasound.

Exclusion criteria: Concurrent disease or infection that could affect platelets count. Causes of splenomegaly other than portal hypertension. History of upper GI bleeding or endoscopic intervention. Known hepatocellular carcinoma (HCC) patient or presence of hepatic focal lesion in pelviabdominal ultrasound. Patients treated with beta blockers.

Methods:

All the patients were subjected to:

Thorough history taking including age, sex, comorbidities, manifestations of liver cell failure, drug history and history of alcohol abuse, bilharziasis, coagulation disorder or treatment with anticoagulants.

- Clinical general and local abdominal examination.
- Recent pelvi-abdominal ultrasound to exclude presence of hepatic focal lesion and to detect cirrhosis, splenomegaly and ascites.
- Upper GI endoscopy (diagnostic and therapeutic if needed) to detect and estimate the size of esophageal varices.

Laboratory investigations: Complete blood picture (CBC), prothrombin concentration, INR, serum AFP, albumin, AST, ALT and bilirubin.

AST, ALT, albumin and bilirubin were analyzed on Elecsys Cobas, Chemistry module c501 (Roche Diagnostics GmbH, Germany).

AFP was assayed on Elecsys Cobas immunoassay analyzer. Immunoassay module e601 (Roche Diagnostics GmbH, Germany).

CBC was done on Cell dyn Ruby (Abbott Laboratories, USA).

PT, PC and INR were assayed on Sysmex CS 5100 (Siemens Healthcare, Germany).

Calculations:

- PAP score = (0.038 + INR x 0.383 + AFP (IU/ml) –1 x0.002) – (platelet count (x10 ^{9}) –1 X 0.003).
- AAR = AST (IU/L)/ALT (IU/L).
- APRI = (AST (IU/L)/AST (Upper Limit of Normal) (IU/L))/Platelets (10 ^{9}/L) x 100.
- Calculation of Child-Pugh score and class.
- FIB-4 = [age (years) x AST (IU/L)]/[platelet count (10^{9}/L) x square root ALT (IU/L)].
- Lok score : –5.56 – 0.0089 x platelet count (10 ^{3} /mm^{3}) + 1.26 x (AST/ALT) + 5.27 x INR.

Statistical methods: The statistical package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA) was for data coding and entry. Mean and standard deviationwere used for quantitative data. Unpaired *t*-test was used for group comparisons. Frequency (count) and relative frequency (%) were used to summarize categorical data [15]. The Chi square (X^2) test was used to compare categorical data [16]. The Spearman correlation coefficient was used to examine correlation between quantitative variables [17]. The best cutoff value of significant scores for identification of large varices was determined using a ROC curve and area under curve analysis. Statistical significance was defined as a *p*-value of less than 0.05.

Results

Patients were classified into 2 groups according to endoscopic size of EV:

Group 1: 60 patients had large-sized EV i.e grade III-IV and Group 2: 30 patients had small-medium sized EV i.e grade I-II.

Table (1) shows the demographic and laboratory data of the studied groups. A statistically significant difference was observed in platelet count, AST, ALT and AFP levels.

Table (2) shows a comparison in theChild-Pugh, AAR, APRI, FIB-4 and LOK scores between patients with large EV and the group with small EV. All scores except the novel PAP score displayed a significant discriminating ability between the two patient groups.

Table (3) shows Child-Pugh scores and class distribution among the studied population. Group 1 (large varices group) displayed higher prevalence of Child B and C scores while group 2 (small varices) displayed a higher prevalence of Child A score.

Table (4) shows the diagnostic sensitivity and specificity of Child-Pugh, AAR, APRI, FIB-4 and LOK scores. APRI and FIB-4 demonstrated the best performance among all scores.

Fig. (1) shows a multiple ROC curve depicting the diagnostic performance of CTP, AAR, APRI, FIB-4 and LOK scores.

Table (5) shows the correlation between the PAP score with various laboratory tests and other scores.

PAP score displayed statistically significant positive correlation with total bilirubin, AST, INR, Child-Pugh, APRI, FIB-4 and LOK score. And statistically significant negative correlation with serum albumin.

Table (1): The demographic and laboratory data of the studied groups.

	Large EV (n=60)		Small-medium EV (n=30)		*p*-value
	Mean	SD	Mean	SD	
Age (years)	60.33	7.54	63.50	7.14	0.035
HB (g/dl)	8.44	2.09	8.68	1.71	0.348
PLT (x 10^{3}/cm^{3})	76.07	30.82	182.47	101.04	<0.001
TLC (x 10^{3}/cm^{3})	7.25	3.51	8.61	4.85	0.266
T.BIL (mg/dl)	1.41	1.16	1.69	2.26	0.563
D.BIL (mg/dl)	0.53	0.61	0.79	1.32	0.598
AST (U/l)	70.22	68.55	40.13	22.02	<0.001
ALT (U/l)	40.17	32.61	27.10	12.49	0.022
AFP (U/ml)	16.76	45.69	24.43	75.04	0.047
ALBUMIN (g/dl)	2.84	0.55	2.75	0.50	0.347
INR	1.50	0.47	1.41	0.32	0.310

Table (2): Liver fibrosis scores in the studied groups.

	Large EV (n=60)		Small-medium EV (n=30)		*p*-value
	Mean	SD	Mean	SD	
Child-Pugh	8.57	1.71	7.63	1.77	0.021
AAR	1.90	0.80	1.57	0.63	0.013
APRI	2.25	1.44	0.70	0.47	<0.001
FIB-4	8.98	3.36	3.06	1.85	<0.001
Lok score	0.94	0.11	0.77	0.25	0.002
PAP score	0.62	0.18	0.59	0.13	0.363

Table (3): Child-Pugh score values in the studied groups.

	Large EV (n=60)		Small-medium EV (n=30)		*p*-value
	Count	%	Count	%	
Child-Pugh class:					
A	5	8.3	9	30.0	0.030
B	39	65.0	16	53.3	
C	16	26.7	5	16.7	

Table (4): Performance of liver fibrosis scores in detection of large size varices.

	AUC	*p*-value	95 % CI		Cut-off value	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %	PLR %	NLR %
			Lower Bound	Upper Bound								
Child	0.648	0.021	0.522	0.773	7.5	73.3	53.3	61.11	66.67	63.33	1.57	0.50
AAR	0.661	0.008	0.542	0.780	1.82	51.7	83.3	74.19	62.71	66.67	3.10	0.58
APRI	0.947	<0.001	0.890	1.003	1.45	90	96.7	97.62	91.67	94.44	27.27	0.10
FIB-4	0.951	<0.001	0.899	1.003	4.7	95	93.3	93.48	95.45	94.44	14.18	0.05
Lok	0.700	0.002	0.572	0.828	0.9050	78.3	60	66.04	72.97	68.89	1.96	0.36

AUC: Area under the curve. PPV: Positive Predictive Value. PLR: Positive Likelihood Ratio.
CI: Confidence Interval. NPV: Negative Predictive Value. NLR: Negative Likelihood Ratio.

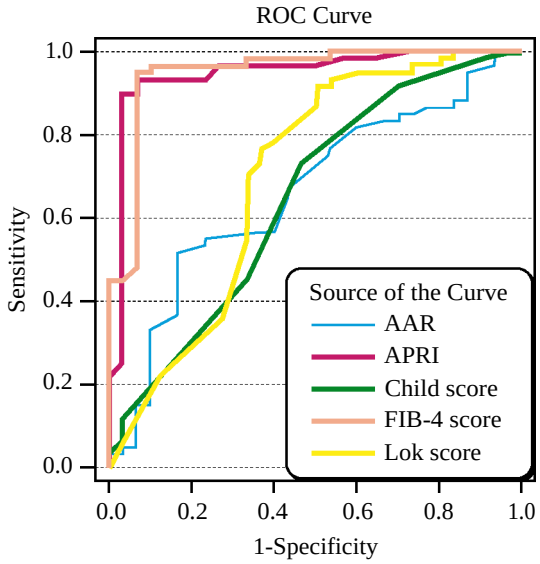

Fig. (1): ROC curve of AAR, APRI, CTP, FIB-4 and Lok scores in detection of large EV.

Table (5): The correlation between the PAP score with various laboratory tests and other scores.

	PAP score	
	Correlation Coefficient	*p*-value
Age	–0.114	0.284
HB	0.126	0.236
PLT	–0.186	0.079
TLC	0.011	0.917
T.BIL	0.458	<0.001
AST	0.279	0.008
ALT	0.163	0.125
AFP	0.056	0.600
ALBUMIN	–0.357	0.001
INR	0.956	< 0.001
Child score	0.419	<0.001
AAR	0.134	0.207
APRI	0.258	0.014
FIB-4 score	0.249	0.018
Lok score	0.816	<0.001

Discussion

The necessity of having a non-invasive, screeningmethod is especially important in countries like Egypt, where endoscopy is not widely accessible and there is a great demand for resource optimization. If the screening non-invasive tests are trustworthy to stratify EV and differentiate between small and large sized ones, targeted screening gastroduodenoscopy may be more cost-effective and less invasive than generalized screening endoscopy. The findings of the current study propose that several non-invasive approaches that are readily accessible in clinical practice could be useful in screening for EV and reducing the frequency of gastroduodenoscopies used in cirrhotic patients' EV care. The reason for adapting basic, non-invasive blood testing used to detect hepatic fibrosis, to the detection of EV was that EV is primarily caused by fibrosis and consequentlyportal hypertension **[18]**. The diagnostic performance of a new score titled PAP score in detecting large EV, was investigated in this study as well as AAR, APRI, FIB-4, Lok, and Child-Pugh scores.

PAP score is based on platelets, alpha AFP and INR. It was developed for discrimination of large-sized EVs (Grade III-IV) in HCV-induced cirrhotic patients **[19]**. There were no other available studies for evaluation of this score. Regarding utility of PAP score in detection of large EV, it had poor diagnostic performance in the current study, there was no statistically significant difference in the mean values of the PAP score when comparing patients with large EV versus small EV group (*p*-value 0.356). That contradicts the findings of the original study which reported that PAP-score anticipated large EVs. It had 77% sensitivity, 86% specificity, 56% PPV, 94% NPV using a cut-off (0.27).

Regarding Fibrosis-4 score (FIB-4) In chronic HCV and NAFLD it was shown to be a useful non-invasive indicator of fibrosis **[20,21]**. It is based on age, AST-ALT values, and platelet count, all of

which are regularly evaluated and obtainable in almost all patients with cirrhosis.

Regarding performance of FIB-4 in discrimination of large EV in the current study, it had the best diagnostic performance among all other scores. At cut-off value of 4.7, It had AUC 0.951, p-value <0.001 with 95% sensitivity, 93.3% specificity and 94.44% accuracy. Upon reviewing the published literature regarding this score's performance, the performance reported in this study was found to be better than most reported studies. Early studies in 2010 **[22]** used a cut off of 4.3 which had AUC 0.6 with 68% sensitivity, 57% specificity and 63% accuracy for prediction of large EV in retrospective set. Later study using a higher cutoff value for predicting large EV(23) a cut off value (6.75) was used, the AUC was 0.628, sensitivity 46% Specificity 77%. Newer research **[24]** reported a better AUC of FIB-4 for large EVs in a large retrospective study (0.7095). Research conducted in 2017 **[25]** showed AUC for large EVs (0.81) at a cut off value >3.4 with sensitivity 78.3, specificity 74.2 and 76.6% accuracy. And most recently a work conducted in 2020, **[26]** used a cut off value >8.92 with AUC for large EVs (0.64) with a sensitivity of 60% and specificity of 65.5%.

Aspartate aminotransferase to platelet ratio index (APRI), Regarding performance of APRI in discrimination of large EV,in this studyit was found that at a cutoff value of 1.45, APRI score had AUC 0.947 with 90% sensitivity, 96.7% specificity, and 94.44% accuracy. APRI performance in this study was better than that reported in other studies. Going through the literature, reviewing APRI utility in detection, as early as 2008 **[27]**, research showed a relation between significant portal hypertension and APRI but no direct correlation with EV. Research **[28]** suggested the cutoff of 1.3 and found that APRI had a 64% specificity, a 68% sensitivity, a 78% NPV and a 51% PPV for predicting EV in HCV-induced Child A patients. A multicenter, large scale trial **[22]** used a cut off of 1.5 which had AUC 0.6 with 54% sensitivity, 63% specificity, and accuracy of 61% for discriminating large EV in retrospective set. Slightly more encouraging results were observed **[29]** using a cutoff value of >1.3, APRI had a PPV of 86.50 %, and an NPV of 43.20% and a sensitivity of 64.7 percent for predicting EV in cirrhotic patients who were categorized as Child A, B, or C. The results of the meta-analysis study (24), reported AUC of APRI for large EVs (0.51) at a cut off value of 0.85. Study by Hassan et al., **[25]** showed AUC for large EVs (0.79) at a cut off of 1.22 with 77.9% accuracy, that closely resembled the earlier results **[30]** and later results **[31]**. Andmost recently in 2020, **[26]** used a cut off of >2.02 with AUC for large EVs (0.7).

Another score evaluated in the current study was Lok index. This score was proposed during the Hepatitis C Antiviral Long-term Treatment against Cirrhosis (Halt-C) trial. It can be used to accurately anticipate histological cirrhosis in patients with chronic hepatitis C and advanced fibrosis **[32]**. Regarding ability of Lok index in discrimination of large EV, at a cut-off value of 0.9050, Lok score had AUC 0.700 with 78.3% sensitivity, 60% specificity, 66.04% and 68.89% accuracy. Lok has a moderate diagnostic accuracy in our study, which resembles the results of the meta-analysis study **[24]**, which reported AUC of Lok for large EVs (0.7264). For predicting EV, **[23]** used a cut off value of >0.62 and the AUC was 0.69; for detection of large EV, while at a cut off value of (0.796), AUC was 0.731. The AUC for the presence of EV and large EV, respectively, were 0.81 and 0.87, according to **[28]**. Again, in the multicenter large scale trial, **[22]** using a cut off of 1.5 which had AUC 0.71 with 74% sensitivity, 63% specificity, 36% PPV, and 70% accuracy for prediction of large EV in retrospective set and excellent NPV of 96% to exclude existence of large EV. And most recently **[26]** used a cut off of>0.99 with AUC for large EVs (0.6).

The fourth fibrosis score evaluated in this study was the AST/ALT ratio (AAR) whichhas been proposed to detect cirrhosis. In a retrospective study **[33]** AST/ALT ratio was significantly higher in patients who had varices compared to those without (ratio: 1.8 versus 1.0, p<0.0001) which prompted further studies to evaluate its performance in the differentiation of large EV. Regarding performance of AAR in discrimination of large EV, in the current study, it was found that at a cut off value of 1.82, it had AUC 0.661 with 51.7% sensitivity, 83.3% specificity, and 66.67% accuracy. The moderate diagnostic accuracy of AAR in this study resembles the results of the meta-analysis study **[24]**, which reported AUC of AAR for large EV (0.60). Another work **[25]** demonstrated AUC for large EVs (0.68) at a cut off of >0.74 with 65% accuracy, that resembles the results of **[34]**. Also, multicenter study **[22]**, used a cut off of 1.1 which had AUC 0.61 with 68% sensitivity, 53% specificity, 56% accuracy for prediction of large EV in retrospective set. Research in 2020 **[26]** used a cut off of >1.89 with AUC for large EVs (0.47). However, for detection of large EV, **[28]** employed a cut-off of 1.0, which resulted in a 68 % sensitivity, 77% specificity, with an AUC of 0.79. Studies that

involved patients with various causes of liver disease and employed variable AST/ALT ratio cutoffs, were unable to reliably detect the existence of EV in clinical practice.

Child-Pugh score (CTP) Child and Turcotte were the first to suggest it to anticipate surgical risk in patients having portosystemic shunt surgery for variceal hemorrhage [35]. It was later modified byomitting nutritional status and adding prothrombin [36]. The Child-Pugh score has been frequently used in practice to determine the severity of cirrhosis, although there is no consistent association between the Child-Pugh score and esophageal varices as was reported by some researchers who found no link between EV and CTP [37,38,39]. Regarding performance of CTP in discrimination of large EV, in the present study, it was found that at cut-off value of 7.5, It had AUC 0.648 with 73.3% sensitivity, 53.3% specificity, and 63.33% accuracy. The percentage of large varices in the current study was considerably higher in Child B patients (65%) than in Child C patients (26.7%), p=0.030. This result is in agreement with (40). On the contrary, [41] found that possibility of esophageal varices or large EVs in Child-Pugh B or C cirrhotic patients, were nearly three times more than Child-Pugh class A. In the current study there was a considerable statistical increase in Child score and the Child class between grades of EV, this is in line with the results of [42] who reported a correlation between the existence of varices and a higher Child score. This again is in agreement with the study [43] thatreported higher grades of varices with Child-Pugh class B/C and spleen diameter as well as another study [44] that reported that lower platelet count and advanced ChildPugh class are predictors of large varices. And a more recent work [45] that used Child score to differentiate between risky and non-risky EV at a cut off value of >8.5, with 95% sensitivity, 80% specificity, 82.6% PPV and 94.1% NPV.

And finally, going over publications from the past 5 years until the present time of writing this work, the following was found. According to [46] a total of 46,014 patients underwent upper gastrointestinal endoscopy for prediction of varices perse, for whom Lok index, Bonacini score, and FIB-4 were calculated. The investigators came to the conclusion that; using non-invasive markers is of limited use in prediction of esophageal varices. Furthermore, the limited accuracymay hinder the use of appropriate primary prophylaxis against variceal bleeding. On the other hand an earlier work utilizing APRI score in pediatric population to assess patients at risk of bleeding came to a more optimistic conclusion that APRI score has an acceptable sensitivity as a marker to delineate high risk varices and avoid unnecessary endoscopy [47].

Conclusion: Although endoscopy continues for nowto be the diagnostic gold standard of esophageal varices, the results of our study suggest that fibrosis scores such as FIB-4, APRI, Lok, AAR and Child-Pugh scores, were significantly able to discriminate patients with large-sized EV. The diagnostic performance of a new PAP score on the other hand in detection of large EV had displayed a poor diagnostic performance in comparison to other liver fibrosis scores. Laboratory tests employed in score calculations are easily available in routine clinical practice and may have a role in screeningof EV, in order to reduce the number of endoscopies needed for management of EV. Non-invasive screening methods could stratify patients into those who are at low risk of harboring clinically relevant EV and do not need primary prophylaxis with beta-blockers and those with large EV. However, available data from different research work done, upon comprehensive review during conducting this work came back with varying results. These results so far do not allow for the replacement of endoscopy in EV screening. On the long run, may be using different combination of scores may help in assigning cirrhotic patient into risk classes and possibly reducing the number of endoscopies needed.

References

1- OMRAN D., ALBORAIE M., ZAYED R.A., et al.: Towards hepatitis C virus elimination: Egyptian experience, achievements and limitations. World J. Gastroenterol., 24 (38): 4330-4340, 2018.

2- ZHANG W., WANG L., WANG L., LI G., HUANG A., YIN P., YANG Z., LING C. and WANG L.: Liver stiffness measurement, better than APRI, Fibroindex, Fib-4, and NBI gastroscopy, predicts portal hypertension in patients with cirrhosis. Cell Biochem. Biophys, 71: 865-873, 2015.

3- GBD 2017 Cirrhosis Collaborators. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol. Hepatol., 5: 245-66, 2020.

4- SANYAL A.J. and SHAH V.H.: Portal Hypertension: Pathobiology, Evaluation, and Treatment, Humana Press, Totowa, NJ, 2005.

5- SINGLA S. and SHAH V.: Portal hypertension. In: SPS Monga, editor. Molecular pathology of liver diseases. Vol. 5. New York: Molecular Pathology Library: Springer, p 485- 496, 2011.

6- D'AMICO G. and DE FRANCHIS R.: Upper digestive bleeding in cirrhosis. Post therapeutic outcome and prognostic indicators. Hepatology, 38: 599-612, 2003.

7- KOVALAK M., LAKE J., MATTEK N., EISEN G., LIEBERMAN D. and ZAMAN A.: Endoscopic screening for varices in cirrhotic patients: Data from a national endoscopic database. Gastrointest Endosc., 65: 82-88, 2007.

8- GARCIA-TSAO G., ABRALDES J.G., BERZIGOTTI A. and BOSCH J.: Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. Hepatology, Jan. 65 (1): 310-335, 2017.

9- KRYSTALLIS C., MASTERTON G.S., HAYES P.C. and PLEVRIS J.N.: Update of endoscopy in liver disease: More than just treating varices. World J. Gastroenterol., 18 (5): 401-411, 2012.

10- ABRALDES J.G., BUREAU C., STEFANESCU H., AUGUSTIN S., NEY M., BLASCO H., PROCOPET B., BOSCH J., GENESCA J. and BERZIGOTTI A.: Anticipate Investigators. Noninvasive tools and risk of clinically significant portal hypertension and varices in compensated cirrhosis: The "Anticipate" study. Hepatology, Dec. 64 (6): 2173-2184, 2016.

11- AUGUSTIN S., MUNTANER L., ALTAMIRANO J.T., GONZÁLEZ A., SAPERAS E., DOT J., ABU-SUBOH M., ARMENGOL J.R., MALAGELADA J.R., ESTEBAN R., GUARDIA J. and GENESCÀ J.: Predicting early mortality after acute variceal hemorrhage based on classification and regression tree analysis. Clin. Gastroenterol. Hepatol., Dec. 7 (12): 1347-54, 2009.

12- BOSCH J. and GARCIA-PAGAN J.C.: Prevention of variceal rebleeding. Lancet, 361: 952-954, 2003.

13- DE FRANCHIS R.: Baveno VI Faculty. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. J. Hepatol., Sep. 63 (3): 743-52, 2015.

14- MERLI M., NICOLINI G., ANGELONI S., RINALDI V., DE SANTIS A., MERKEL C., ATTILI A.F. and RIGGIO O.: Incidence and natural history of small esophageal varices in cirrhotic patients. J. Hepatol., Mar. 38 (3): 266-72, 2003.

15- CHAN Y.H.: Biostatistics102: Quantitative Data - Parametric & Non-parametric Tests. Singapore Med. J., 44 (8): 391-396, 2003.

16- CHAN Y.H.: Biostatistics 103: Qualitative Data -Tests of Independence. Singapore Med. J., 44 (10): 498-503, 2003.

17- CHAN Y.H.: Biostatistics 104: Correlational Analysis. Singapore Med. J., 44 (12): 614-619, 2003.

18- SANYAL A., BOSCH J., BLEI A. and ARROYO V.: Portal hypertension and its complications. Gastroenterology, 134: 1715-1728, 2008.

19- FARID K., OMRAN M.M., FARAG R.E., ARAFA M.M. and EMRAN T.M.: Development and evaluation of a novel score for prediction of large oesophageal varices in patients with hepatitis c virusinduced liver cirrhosis. Br. J. Biomed Sci., Jul. 74 (3): 138-143, 2017.

20- VALLET-PICHARD A., MALLET V., NALPAS B., VERKARRE V., NALPAS A., DHALLUIN-VENIER V., FONTAINE H. and POL S.: FIB-4: An inexpensive and accurate marker of fibrosis in HCV infection. comparison with liver biopsy and fibrotest. Hepatology, Jul. 46 (1): 32-6, 2007.

21- HARRISON S.A., OLIVER D., ARNOLD H.L., GOGIA S. and NEUSCHWANDER-TETRI B.A.: Development and validation of a simple NAFLD clinical scoring system for identifying patients without advanced disease. Gut., 57 (10): 1441-1447, 2008.

22- SEBASTIANI G., TEMPESTA D., FATTOVICH G., CASTERA L., HALFON P., BOURLIERE M., NOVENTA F., ANGELI P., SAGGIORO A. and ALBERTI A.: Prediction of oesophageal varices in hepatic cirrhosis by simple serum non-invasive markers: Results of a multicenter, large-scale study. J. Hepatol., Oct. 53 (4): 630-8, 2010.

23- STEFANESCU H., GRIGORESCU M., LUPSOR M., MANIU A., CRISAN D., PROCOPET B., et al.: A new and simple algorithm for the noninvasive assessment of esophageal varices in cirrhotic patients using serum fibrosis markers and transient elastography. J. Gastrointestin Liver Dis., 20: 57-64, 2011.

24- DENG H., QI X., PENG Y., LI J., LI H., ZHANG Y., LIU X., SUN X. and GUO X.: Diagnostic Accuracy of APRI, AAR, FIB-4, FI, and King Scores for Diagnosis of Esophageal Varices in Liver Cirrhosis: A Retrospective Study. Med. Sci. Monit., Dec 20 (21): 3961-77, 2015.

25- HASSAN E., EL-DIN S., SHARAF A., et al.: Noninvasive Fibrosis Scores as Prognostic Markers for Varices Needing Treatment in Advanced Compensated Liver Cirrhosis. Open Journal of Gastroenterology, 7: 230-42, 2017.

26- PANDEY R., PATHAK R., GNAWALI A., KHADGA P., SHARMA S., JHA A., HAMAL R., KOIRALA D. and PARAJULI P.: Diagnostic Accuracy of Non-invasive Laboratory-Based Fibrosis Scores in Predicting the Presence of Esophageal Varices in Liver Cirrhosis. Journal of Advances in Internal Medicine, 9 (2): 54-59, 2020.

27- BERZIGOTTI A., GILABERT R., ABRALDES J.G., NICOLAU C., BRU C., BOSCH J. and GARCÍA-PAGAN J.C.: Noninvasive prediction of clinically significant portal hypertension and esophageal varices in patients with compensated liver cirrhosis. Am. J. Gastroenterol., May 103 (5): 1159-67, 2008.

28- CASTÉRA L., LE BAIL B., ROUDOT-THORAVAL F., BERNARD P.H., FOUCHER J., MERROUCHE W., COUZIGOU P. and DE LÉDINGHEN V.: Early detection in routine clinical practice of cirrhosis and oesophageal varices in chronic hepatitis C: Comparison of transient elastography (FibroScan) with standard laboratory tests and non-invasive scores. J. Hepatol., Jan. 50 (1): 59-68, 2009.

29- MATTOS A.Z., ALVES DE MATTOS A., DAROS L.F. and MUSSKOPF M.I.: Aspartate amino transferase-to platelet ratio index (APRI) for the non-invasive prediction of esophageal varices. Ann. Hepatol., Sep-Oct. 12 (5): 810-4, 2013.

30- MORISHITA N., HIRAMATSU N., OZE T., et al.: Liver stiffness measurement by acoustic radiation force impulse is useful in predicting the presence of esophageal varices or high risk esophageal varices among patients with HCV-related cirrhosis. J. Gastroenterol., 49 (7): 1175-82, 2014.

31- ZHANG F. and LIU T.: Predictive Value of a Noninvasive Serological Hepatic Fibrosis Scoring System in Cirrhosis

Combined with Oesophageal Varices. Can J. Gastroenterol. Hepatol., 2018: 7671508, 2018.

32- LOK A.S., GHANY M.G., GOODMAN Z.D., WRIGHT E.C., EVERSON G.T., STERLING R.K., EVERHART J.E., LINDSAY K.L., BONKOVSKY H.L., DI BISCEGLIE A.M., LEE W.M., MORGAN T.R., DIENSTAG J.L. and MORISHIMA C.: Predicting cirrhosis in patients with hepatitis C based on standard laboratory tests: Results of the HALT-C cohort. Hepatology, Aug. 42 (2): 282-92, 2005.

33- NYBLOM H., BJÖRNSSON E., SIMRÉN M., ALDENBORG F., ALMER S. and OLSSON R.: The AST/ALT ratio as an indicator of cirrhosis in patients with PBC. Liver International, 26 (7): 840-845, 2006.

34- CALVARUSO V., BRONTE F., CONTE E., SIMONE F., CRAXÌ A. and DI MARCO V.: Modified spleen stiffness measurement by transient elastography is associated with presence of large oesophageal varices in patients with compensated hepatitis C virus cirrhosis. J. Viral Hepat., Dec. 20 (12): 867-74, 2013.

35- CHILD C.G. and TURCOTTE J.G.: Surgery and portal hypertension. Major Probl. Clin. Surg., 1: 1-85, 1964

36- PUGH R.N., MURRAY-LYON I.M., DAWSON J.L., PIETRONI M.C. and WILLIAMS R.: Transection of the oesophagus for bleeding oesophageal varices. Br. J. Surg., 60: 646-9, 1973.

37- CHALASANI N., KAHI C., FRANCOIS F., PINTO A., MARATHE A., BINI E.J., PANDYA P., SITARAMAN S. and SHEN J.: Model for end-stage liver disease (MELD) for predicting mortality in patients with acute variceal bleeding. Hepatology, May 35 (5): 1282-4, 2002.

38- BENEDETO-STOJANOV D., NAGORNI A., BJELAKOVIC G., STOJANOV D., MLADENOVIC B. and DJENIC N.: The Model for the End-Stage Liver Disease and Child-Pugh score in predicting prognosis in patients with liver cirrhosis and esophageal variceal bleeding. Vojnosanit Pregl., 66 (9): 724-8, 2009.

39- FLORES-RENDON A.R., GONZALEZ-GONZALEZ J.A., GARCIA-COMPEAN D., MALDONADO-GARZA H.J. and GARZA-GALINDO A.A.: Model for end stage of liver disease (MELD) is better than the Child-Pugh score for predicting in hospital mortality related to esophageal variceal bleeding. Ann. Hepatol., 7 (3): 230-4, 2008.

40- THOMOPOULOS K.C., LABROPOULOU K.C., MIMIDIS K.P., KATSAKOULIS E.C., ICONOMOU G. and NIKOLOPOULOU V.N.: Non-Invasive predictors of the presence of large esophageal varices in patients with cirrhosis. Dig and Liver Dis., 35: 473-8, 2003.

41- ZAMAN A., BECKER T., LAPIDUS J. and BENNER K.: Risk factors for the presence of varices in cirrhotic patients without a history of variceal hemorrhage. Arch. Intern. Med., Nov. 26; 161 (21): 2564-70, 2001.

42- MADHOTRA R., MULCAHY H.E., WILLNER I. and REUBEN A.: Prediction of esophageal varices in patients with cirrhosis. J. Clin. Gastroenterol., Jan. 34 (1): 81-5, 2002.

43- CHERIAN J.V., DEEPAK N., PONNUSAMY R.P., SOMASUNDARAM A. and JAYANTHI V.: Non-invasive predictors of esophageal varices. Saudi J. Gastroenterol., Jan-Feb. 17 (1): 64-8, 2011.

44- BURTON J.R., LIANGPUNSAKUL S. and LAPIDUS J.: Validation of a multivariate model predicting presence and size of varices. Journal of Clinical Gastroenterology, 41 (6): 609-615, 2007.

45- GOMAA A., MOHAMMED S., MOUSA W., HASAN N. and MHDY M.: Evaluation of ALBI, MELD and Child-Pugh Scores as non-Invasive Predictors of Esophageal Varices. The Egyptian Journal of Hospital Medicine, 73 (8): 7358-7364, 2018.

46- MOHAMED EL-KASSAS, WAFAA ELAKEL, MOHAMED ALBORAIE, REEM EZZAT, SARA ABDELHAKAM, MOHAMED HASSANY, ZAINAB ALIELDIN, AHMED F. SHERIEF, AYMAN YOSRY, MAGDY EL-SERAFY, MANAL HAMDY EL-SAYED, IMAM WAKED, WAHID DOSS and GAMAL ESMAT: Egyptian National Committee for Control of Viral Hepatitis. Egyptian revalidation of non-invasive parameters for predicting esophageal varices in cirrhotic patients: A retrospective study. Arab J. Gastroenterol., May 23 (2): 120-124, 2022.

47- JOSÉ RICARDO BORÉM LOPES, ALEXANDRE RODRIGUES FERREIRA, PRISCILA MENEZES FERRI LIU, THAÍS COSTA NASCENTES QUEIROZ, ELEONORA DRUVE TAVARES FAGUNDES, JÚLIO ROCHA PIMENTA, JOSÉ ANDRADE FRANCO NETO, SIMONE DINIZ CARVALHO, MARIA EDUARDA MARQUES BORGES and LUCAS GARCIA DE FIGUEIREDO COLIN: Non-invasive Predictors of Esophageal Varices With a High Risk of Bleeding in Pediatric Cirrhotic Patients. J. Pediatr. Gastroenterol. Nutr., Jun. 1; 72 (6): 802-806, 2021.

تقييم PAP وقياسات التليف كبدى الغير تداخلى لمنظار الجهاز الهضمى العلوى فى الكشف عن دوالى المرئ كبيرة الحجم فى مرضى التليف الكبدى الناتج عن فيروس الالتهاب الكبدى (ج)

تليف الكبد هو المرحلة النهائية من مرض الكبد المزمن، ويسبب ارتفاع ضغط الدم البابى وهو العا مل الرئيسى فى تكوين دوالى المرئ. وهم عرضة للتمزق والنزيف ويعتبر تنظير الجهاز الهضمى العلوى هو المعيار الذهبى فى الكشف لأنه يسمح بإ كتشاف المرضى المعرضين لخطر النزيف. طرق الكشف غير التداخلية يمكن أن تفرق بين المرضى المعرضين لخطر منخفض جداً للإصابة بدوالى المرئ ذات الأهمية الإكلينيكية والذين لايحتاجون إلى الوقاية الأولية وهؤلاء الذين يعانون من دوالى المرئ الكبيرة الحجم.

المواد والأساليب : اشتملت هذه الدراسة على ٩٠ مريضاً من مرضى التليف الكبدى الناجم عن التهاب الكبد الوبائى (ج).

– المجموعة الأولى : ٦٠مريضاً لديهم دوالى مرئ كبيرة الحجم، أى من الدرجة الثالثة إلى الرابعة.

– المجموعة الثانية : ٣٠ مريضاً لديهم دوالى مرئ صغيرة الحجم، أى من الدرجة الأولى إلى الثانية.

تم إخضاعهم لفحص التاريخ الطبى والفحص السريرى والفحوصات المخبرية وموجات فوق الصوتية حديثة للحوض والبطن وحساب مجاميع النقاط الآتية وتقييم أدائها التشخيصى فى الكشف عن دوالى المرئ كبيرة الحجم Lok وChild-Pugh وFib-4و APRI وAAR وPAP.

النتائج : قمنا بتقييم الأداء التشخيصى لمجموع (PAP) وقد كان أدائها التشخيصى ضعيفاً فى دراستنا، مقارنة بباقى القياسات المعملية لتليف الكبد مثل Lok، FIB-4، APRI، AAR–Child-Pugh.

الاستنتاج : قد يكون لطرق لفحص غير التداخلية قيمة فى إكتشاف المرضى الذين يعانون من دوالى المرئ كبيرة الحجم والذين يحتاجون إلى الوقاية الأولية باستخدام حاصراتبيتا. ولكن لا تسمح البيانات المتاحة باستبدال التنظير الداخلى فى الكشف عن دوالى المرئ، لكنها قد تساعد فى التقسيم الطبقى لمرضى التليف الكبدى حسب فئة الخطورة وربما تقليل عدد التنظير الداخلى المطلوب.