Evaluation Of Fibroscan And Serum Fibrosis Markers Role To Predict The Presence Of Esophageal Varices In Compensated Cirrhosis Patients

*Dr.Jasim M Ghadhban
**Dr.IssamAbdulkarim Selman
*** Dr.Jawad Alkagany

ABSTRACT

Background: Variceal bleeding is a major complication of liver cirrhosis.Early detection of these varices is very important for the prevention of bleeding episode.noninvasive tools can predict portal hypertension progression and occurrence of esophageal varices. It was proposed that liver stiffness measured by fibroscan, may not only predict fibrosis and portal pressure but may also predict the presence and absence of esophageal varices in cirrhotic patients. **Aim:**The aim of this study is to evaluate the performance and diagnostic accuracy offibroscan and serum fibrosis markers to predict the presence esophageal varices in cirrhotic patients. **Methods:**A cross sectional study in which 108 patients with compensated liver cirrhosis were included. Routine laboratory investigations were done, and APRI, FIB-4, and Lok Scores were measured. Every participants were subjected to fibroscan and upper endoscopy. The performance of these methods was evaluated by using sensitivity, specificity , positive predictive value, negative predictive value, accuracy, and receiver operating characteristic curves and then optimal cutoff were estimated.**Results:**Liver stiffness measurement by fibroscan was significantly associated with the presence of esophageal varices (40.39KPa in patients with esophageal varices versus 19.7KPa in patients without varices, and the P value= <0.0001). Using a liver stiffness cutoff of 20kPa for predicting the presence of esophageal varices the AUROC was 0.868 indicating significant association between higher readings of fibroscan result and the presence of esophageal varices. Fibroscan results was 89.2% sensitive, 76.5% specific, and 85.2% accurate for predicting the presence of esophageal varices.The Lok score performed best among serum fibrosis markers for predicting the presence of esophageal varices, for a cutoff of 0.54 the AUROC was 0.846 and it was 75.7% sensitive, 82.4% specific, and 77.8% accurate for predicting of esophageal varices. With combination of fibroscan and Lok score cutoffs the accuracy increased to 87.0%, sensitivity increased to 94.6%, while the specificity decreased to 70.6%. **Conclusion:**Fibroscan and Lok Score are good noninvasive predictors for excluding the presence of esophageal varices in patients with compensated liver cirrhosis.

Keywords: Transient elastography, Fibroscan, Noninvasive , Liver cirrhosis , Esophageal varices, Serum fibrosis markers, Lok score.

Introduction:

Variceal bleeding is one of the major complications of liver cirrhosis and Early detection of these varices is very important for the prevention of bleeding .Esophageal varices may occur in up to 90% of patients with liver cirrhosis[1] .The incidence of bleeding from esophageal varices is about 5% in patients who had small and 15% in patients with large esophageal varices. For each bleeding event mortality is around 10-20%. And survival per one year is 63%[2,3,4].

Esophageal varices occurs in 40% of patients with compensated cirrhosis and up to 60% of patients with decompensated cirrhosis,

with a constant progressive evolution; and when detected, patients should undergo regular surveillance[5]. Primary prevention for bleeding esophageal varices is highly effective, and this required that all patients with compensated cirrhosis should have adequate detection of esophageal varices[6].

The current guideline for screening patients with liver cirrhosis for esophageal varices is to perform endoscopy at 2to3 years in patients lacking esophageal varices and at interval of 1to2 years in patients with small varices[7].

*MBCHB , CABM , FICM (GE & H),Consultant of Gastrointestinal endoscopy, President of ISGH
**C.A.B.M., F.I.C.M.S (GE&H)/Gastroenterology & Hepatology teaching hospital/Medical City Complex/Baghdad/Iraq
***C.A.B.M., F.I.C.M.S.the gatroenterology & hepatology teaching hospital

The current recommendations cause considerable load and expense to endoscopy units and are frequently poorly tolerated by patients who may decline further follow-up when not done under general anesthesia or deep sedation[8].For these considerations, selection was proposed using multiple non-invasive methods for patients with a high possibility of having esophageal varices[9].

Transient elastography (fibroscan) was identified as a rapid, noninvasive method for assessing the extent of liver disease, and was considered effective in recent studies in identifying the underlying stage of fibrosis [10,11,12]. Thus, fibroscan has the capability of being used for the noninvasive assessment of esophageal varices [13].

Noninvasive serum markers of liver fibrosis like APRI, Fib-4, and Lok Score, were evaluated as predictors of EV in cirrhotic patients with impressive results which is based on the idea that the development of portal hypertension is attributable to liver fibrosis, as being the most significant factor contributing to the increase hepatic resistance. Many studies have already been conducted [14, 15].

The aim of this study is to estimate and to define the diagnostic accuracy of fibroscan and serum fibrosis markers; Fib-4, APRI and Lok Score as noninvasive predictors of the presence esophageal varices in patients with liver cirrhosis.

Patients And Methods:

In This cross sectional study a total of 108 patients with compensated liver cirrhosis were consecutively included in the period from January 2020 to May 2020.Diagnosis of liver cirrhosis was established by clinical, laboratory and imaging (ultrasound or other imaging modality).

Inclusion criteria: Adult patients more than 18 years with compensated liver cirrhosis and no previous history of upper GIT bleeding.

Exclusion criteria: Patients age less than18 years, Liver cirrhosis with ascites, History of previous upper GIT bleeding, hepatocellular carcinoma, portal vein thrombosis, acute liver failure and patient who were treated with B-blocker or experienced sclerotherapy or band ligation.

All the patients performed routine laboratory tests, serum fibrosis markers were measured, and they underwent liver stiffness measurement by fibroscan, then they were subjected to upper gastrointestinal endoscopy for screening for EV.

Routine laboratory tests were recorded,These laboratory tests are total bilirubin (TSB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), international normalized ratio (INR), prothrombin time (PT), platelets count, serum albumin, then Child-Pugh score was calculated.

Serum liver fibrosis scores had been performed in all patients using their previously published formulas:

- AST to platelets ratio index (APRI) = "[(AST/ULN) x 100]/platelet count 109/L (ULN= the upper limit of normal)"[16].
- FiB4 = "[age (years) x AST (IU/L)]/[platelet count (109/L) x ALT (IU/L)1/2]" [17].
- Lok Score: "log odds = - 5.56 0.0089 x platelet count (103/mm3) + 1.26 x (AST/ALT)+5.27 x INR; Lok = [exp (log odds)]/[1 + exp (log odds)]" [18].

Liver stiffness measurement was done by Fibroscan®530 COMPACT (2018), manufactured by Echosence (30 place d'ltalie, Paris, France).Liver stiffness measurement was considered reliable only if it had 10 successful acquisitions and ,a success rate of more than 60% percent, and with an interquartile range of ≤30 %.

All patients included in this study underwent upper endoscopy, using a flexible EVIS LUCERA video gastroscope (Olympus, Japan) and flexible PENTAX video gastroscope (PENTAX Europe GmbH, Hamburg ,Germany) to detect the presence or absence of esophageal varices.the time between endoscopic examination and liver stiffness measurement was not more than 6 months and was not performed by the same examiner.

The data analyzed using Statistical Package for Social Sciences (SPSS) version 25. The data presented as mean, standard deviation and ranges. Categorical data presented by frequencies and percentages. Independent t-test (two tailed) was used for normally distributed data and Mann-Whitney U test used for not normally distributed data to compare the continuous variables accordingly. Chi square test was used to assess the association between categorical variables, while fisher exact test was used instead when the expected frequency was less than 5. Receiver operating characteristic (ROC) curve analysis was used for prediction of certain continuous variables for diagnosis of presence esophageal varices .

The diagnostic performance of fibroscan and serum fibrosis scores was assessed using sensitivity, specificity, positive predictive value, negative predictive value, and accuracy. A level of P value less than 0.05 was considered significant.

Results:

General characteristics

The general characteristics of patients included in this study is shown in table (1).

Table 1: General characteristics and laboratory findings of patients

Parameter	Range	Mean ± SD or N(%)
Age(years)	19-80	50.44±15
Gender(males/females)		56(51.9)/52(48.1)
Cause of cirrhosis HCV/HBV/Alcohol/others		34(31.5)/30(27.80)/24(22.2)/20(18.5)
Child-Pugh score A/B/C		66(61.1)/38(35.2)/4(3.7)
Endoscopic findings EV yes/no		74(86.5)/34(31.5)
Platelet count(10^9/L)	23.0 – 437.0	146.2 ± 84.6
AST (U/L)	12.0 – 157.0	55.2 ± 30.8
ALT (U/L)	16.0 – 111.0	50.1 ± 26.1
PT (Sec)	9.0 – 27.0	13.7 ± 3.2
INR	0.7 – 2.2	1.09 ± 0.24
TSB (mg/dl)	0.3 – 8.2	1.38 ± 1.4
S. Albumin (g/dl)	1.8 – 4.6	3.28 ± 0.65

Table 2 shows the association between presence of esophageal varices and certain patients characteristics. All patients with cirrhosis and CTP class C had esophageal varices with significant associations (P < 0.05) between esophageal varices and CTP classes. Regarding the cause of liver cirrhosis 91.7% of alcoholic patients had esophageal varices with significant association(P<0.05)between esophageal varices and the cause of cirrhosis. Means of fibroscan, APRI, Fib-4, and Lok score were significantly higher in patients with esophageal varices than that in those without esophageal varices.

Table 2: Association between presence of esophageal varices and certaindermographic and clinical characteristics of patients

Variable	Presence of esophageal varices		Total (%) n= 108	P - Value
	Yes (%)or mean± SD n= 74	No (%)or mean± SD n= 34		
Age (Year)				
<40	14 (58.3)	10 (41.7)	24 (22.2)	
40 – 59	34 (70.8)	14 (29.2)	48 (44.4)	0.471
= 60	26 (72.2)	10 (27.8)	36 (33.3)	
Gender				
Male	36 (69.2)	16 (30.8)	52 (48.1)	0.878
Female	38 (67.9)	18 (32.1)	56 (51.9)	
Cause of liver cirrhosis				
HBV	20 (66.7)	10 (33.3)	30 (27.8)	
HCV	20 (58.8)	14 (41.2)	34 (31.5)	0.042
Alcohol	22 (91.7)	2 (8.3)	24 (22.2)	
Others	12 (60.0)	8 (40.0)	20 (18.5)	
CTP Score				
A	36 (54.5)	30 (45.5)	66 (61.1)	
B	34 (89.5)	4 (10.5)	38 (35.2)	0.0004
C	4 (100.0)	0 (0)	4 (3.7)	
Fibroscan (kPa)	40.39 ± 18.23	19.7 ± 7.0	108	<0.0001
APRI	1.92 ± 1.99	0.88 ± 1.03	108	<0.0001
Fib-4	4.45 ± 2.99	2.05 ± 2.11	108	<0.0001
Lok Score	0.67 ± 0.25	0.27 ± 0.26	108	<0.0001

Performance of Fibroscan, and serum fibrosis scores to detect the presence of esophageal varices
Receiver operating characteristic (ROC) curve analysis was constructed for fibroscan, and serum fibrosis scores, as predictors of presence of esophageal varices. As shown in table (3) and figures (1 and 2) and the cut-off point of fibroscan was 20 kPa, so fibroscan result > 20 kPa is predictive for presence of esophageal varices with a large significant area under the curve (AUC= 86.8%) indicating significant association between higher level of fibroscan result and the presence of esophageal varices.

Fibroscan result was 89.2% sensitive, 76.5% specific, and 85.2% accurate for predicting of esophageal varices.
Lok score was the best among serum fibrosis markers in predicting the presence of esophageal varices, Lok score > 0.54 is predictive for the presence of esophageal varices with a large significant area under the curve (AUC= 84.6%). Lok score result was 75.7% sensitive, 82.4% specific, and 77.8% accurate for predicting of esophageal varices.

Table 3: Diagnostic accuracy of fibroscan, and serum fibrosis scores, as predictors for the presence of esophageal varices

Variable	Cut-off value	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
Fibroscan	20.0	89.2%	76.5%	89.2%	76.5%	85.2%	86.8%
APRI	0.71	89.2%	52.9%	80.5%	69.2%	77.7%	75.2%
Fib-4	2.64	72.9%	76.4%	87.1%	56.5%	74.1%	80.2%
Lok Score	0.54	75.7%	82.4%	90.3%	60.9%	77.8%	84.6%

Analysis of fibroscan and lok score in predicting the presence of esophageal varices
we select the lok score in combination with fibroscan results for further analysis, we combine their cut-off values for predicting the presence of esophageal varices trying to improve the diagnostic accuracy, and we noticed improved sensitivity and NPV without significant decrease in specificity and PPV as shown in table (4).

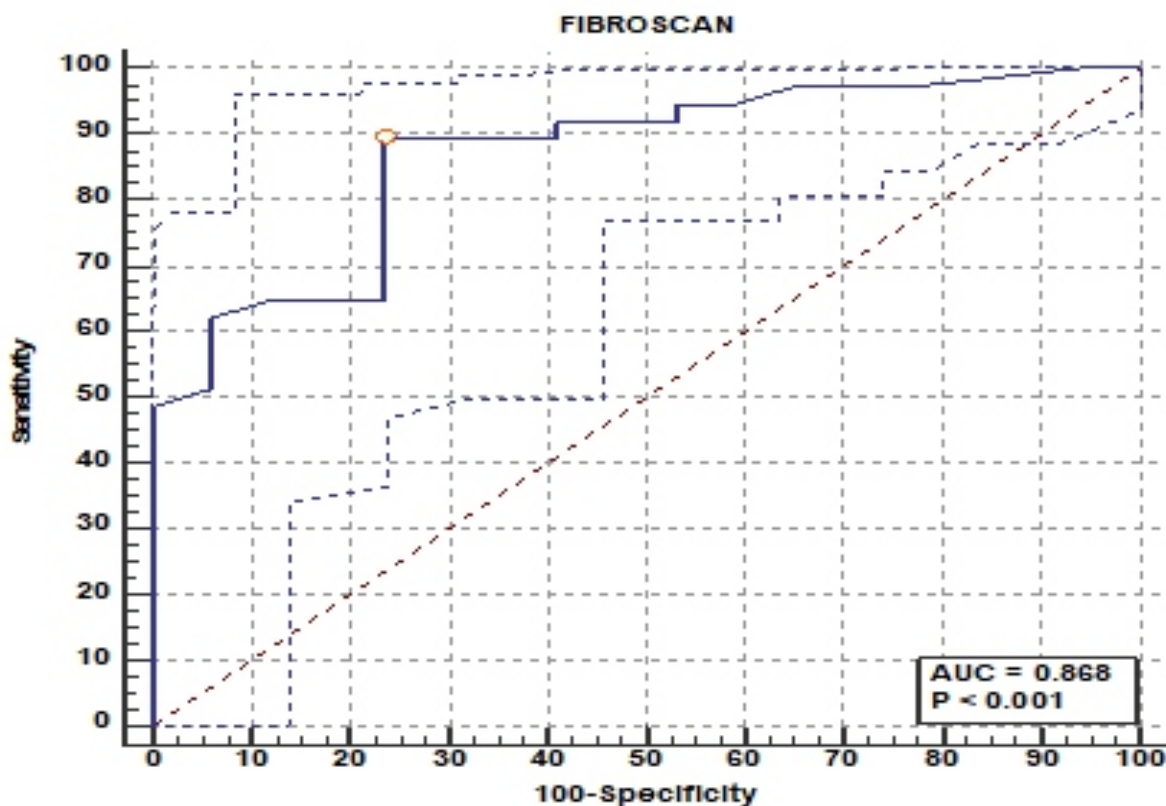Figure 1: ROC curve for fibroscan as a predictor for the presence of esophageal varices

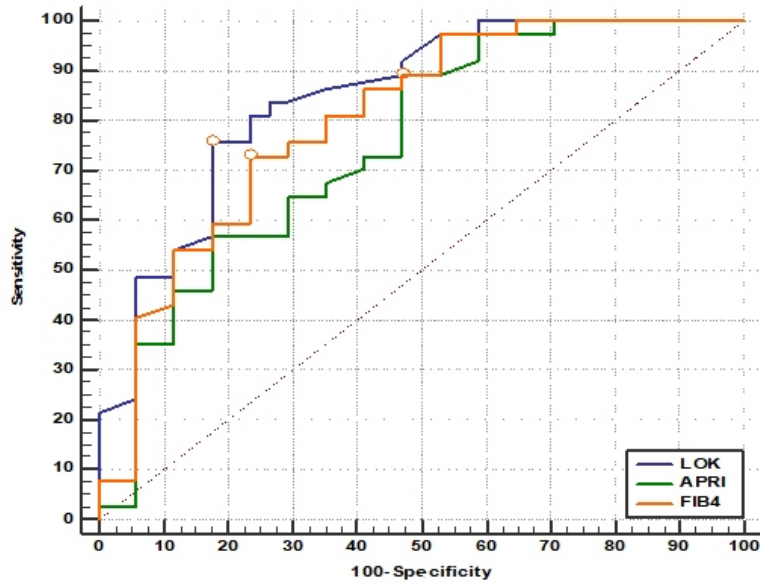Figure 2: ROC curve for serum fibrosis scores as a predictor for the presence of esophageal varices

Table 4: performance of combination of fibroscan and lok score in predicting the presence of esophageal varices

Cut-off value	Fibroscan>20 kPa Lok score> 0.54
Sensitivity	94.6%
Specificity	70.6%
PPV	87.5%
NPV	85.7%
Accuracy	87.0%

Discussion:

Many studies evaluated liver stiffness measurement as a good predictor of presence esophageal varices, with the area under the ROC curve ranging from 0.76 to 0.98 [14,19,20,21--29]. And their proposed cutoff values were ranging from (13.9 kPa to 35 kPa).

The difference between these cut off values may be explained by the heterogeneous etiology conducted by the reviewed studies mentioned above. Pritchatt et al [23] stated that in patient with cirrhosis due to hepatitis C virus the number of false negative cases was significantly higher than in patients without HCV, while Nguyen-Khac et al [26] showed that the cut off value is higher in patients with cirrhosis caused by alcohol (19.5kPa) compared with patients with HCV cirrhosis (12.5-14.6kPa).

In this study we included a more balanced population regarding etiology ,and predominance of alcoholic patients is more in esophageal varices group, and this distribution according to etiology may have had effect on the accuracy of our result. We tried to analyze the cut off values according to the etiology but the lower number of patients made the results inconclusive.

Another limitation in our study is the low number of analyzed cases, and many studies we have reviewed suffer from the same problem [20].

Other source of bias in our study may arise from the numeric inequality between the patients without esophageal varices (34) and patients with esophageal varices (74).

In our study Child Pugh score had been significantly greater in patients with esophageal varices than in those without varices and this is in agreement with Madhotra et al [30].

On the other hand, serum fibrosis markers that had a strong relationship with liver fibrosis was also tried as predictors for the presence of esophageal varices.

The Lok score had been suggested during the Halt-C trial [18]. for a cutoff value less than 0.2 cirrhosis was excluded, whereas for cutoff value greater than 0.5 cirrhosis was confirmed. When used to predict the presence of esophageal varices, it similarly had a good performance. In a large study [57] , for the diagnosis of presence of esophageal varices a cutoff value of 0.9 was suggested with an AUROC of 0.77.
In our study Lok score had the best performance among all serum fibrosis markers that were included in this study. For a cutoff value of 0.54 we had an AUROC of 0.84,sensitivity 75.7%,specifity 82.4%,PPV 90.3%,NPV 60.9% and overall accuracy 77.8% .Combining two distinct noninvasive techniques, for example fibroscan and a serum fibrosis markers, was considered encouraging [31,32].Castera et al indirectly proposed by investigating the differences between fibroscan measurements and serum fibrosis markers,

that the relationship between fibroscan and Lok score would be expected to increase the overall diagnostic performance[33].

In our study, we tried the combination between fibroscan and Lok Score to predict the presence of esophageal varices. When used together, and by using a cutoff value of 20 kPa for fibroscan and 0.54 for Lok score the diagnostic accuracy increased to 87%, sensitivity to 94.6% and NPV to 85.7% which is better than the performance of each test alone and this is in agreement with Stefanescu et al[19].

Conclusion:

Fibroscan and Lok Score are good noninvasive predictors for excluding the presence of esophageal varices in patients with compensated liver cirrhosis. The combination of these two methods for the assessment of the presence of esophageal varices can help to restrict the number of patients selected for endoscopic screening.

References:

1- Jensen DM. Endoscopic screening for varices in cirrhosis: findings, implications, and outcomes. Gastroenterology 2002; 122:1620- 1630.

2- D'Amico G, Criscuoli V, Fili D, Mocciaro F, Pagliaro L. Metaanalysis of trials for variceal bleeding. Hepatology 2002; 36:1023- 1024.

3- Carbonell N, Pauwels A, Serfaty L, Fourdan O, Lévy VG, Poupon R. Improved survival after variceal bleeding in patients with cirrhosis over the past two decades. Hepatology 2004; 40:652659.

4- Stokkeland K, Brandt L, Ekbom A, Hultcrantz R. Improved prognosis for patients hospitalized with esophageal varices in Sweden 19692002. Hepatology 2006; 43:500-505.

5- Schepis F, Cammà C, Niceforo D, et al. which pacients with cirrhosis should undergo endoscopic screening for esophageal varices detection? Hepatology 2001; 33: 333-338.

6- Imperiale TF, Chalasani N. A meta-analysis of endoscopic variceal ligation for primary prophylaxis of esophageal variceal bleeding. Hepatology 2001; 33: 802807.

7- Saad Y, Said M, Idris MO, Rabee A, Zakaria S. Liver stiffness measurement by fibroscan predicts the presence and size of esophageal varices in egyptian patients with HCV related liver cirrhosis. J ClinDiagn Res 2013; 7: 2253-2257.

8- Cales P, Desmorat H, Vinel JP, Caucanas JP, Ravaud A, Gerin P, et al. Incidence of large oesophageal varices in patients with cirrhosis: application to prophylaxis of first bleeding. Gut 1990;31:12981302.

9- de Franchis R. Updating consensus in portal hypertension: report of the Baveno III Consensus Workshop on definitions, methodology and therapeutic strategies in portal hypertension. J Hepatol 2000;33:846852.

10-Shaheen AA, Wan AF, Myers RP. FibroTest and FibroScan for the prediction of hepatitis C-related fibrosis: a systematic review of diagnostic test accuracy. Gastroenterol 2007; 102: 2589-2600.

11- Friedrich-Rust M, Ong MF, Martens S, Sarrazin C, Bojunga J, Zeuzem S, Herrmann E. Performance of transient elastography for the staging of liver fibrosis: a meta-analysis. Gastroenterology 2008; 134: 960-974.

12-Stebbing J, Farouk L, Panos G, Anderson M, Jiao LR, Mandalia S, Bower M, Gazzard B, Nelson M. A meta-analysis of transient elastography for the detection of hepatic fibrosis. J ClinGastroenterol 2010; 44: 214-219.

13-Castera L, Pinzani M, Bosch J. Noninvasive evaluation of portal hypertension using transient elastography. J Hepatol 2012; 56: 696-703.

14-Castera L, Le Bail B, Roudot-Thoraval F, et al. 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 2009; 50:59-68.

15-Sebastiani G, Tempesta D, Fattovich G, et al. Prediction of oesophageal varices in hepatic cirrhosis by simple serum noninvasive markers: Results of a multicenter, large-scale study. J Hepatol 2010; 53:630-638.

16-Wai CT, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 2003; 38: 518-526.

17-Vallet-Pichard A, Mallet V, Nalpas B, et al. FIB-4: an inexpensive and accurate marker of fibrosis in HCV Infection. Comparison with liver biopsy and fibrotest. Hepatology 2007; 46: 32-36.

18-Lok AS, Ghany MG, Goodman ZD, et al. Predicting cirrhosis in patients with hepatitis C based on standard laboratory tests: results of the HALT-C cohort. Hepatology 2005; 42:282-292.

19-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 Gastroin-testin Liver Dis. 2011;20:57-64.

20-Vizzutti F, Arena U, Romanelli RG, et al. Liver stiffness measurement predicts severe portal hypertension in patients with HCV-related cirrhosis. Hepatology 2007; 45: 12901297.

21-Castera L, Forns X, Alberti A. Non-invasive evaluation of liver fibrosis using transient elastography. J Hepatol 2008; 48: 835 847.

22-Kazemi F, Kettaneh A, N'Kontchou G, et al. Liver stiffness measurement selects patients with cirrhosis at risk of bearing large esophageal varices. J. Hepatol. 2006; 45: 230235.

23- Pritchett S, Cardenas A, Manning D, Curry M, Afdhal NH. The optimal cut-off for predicting large oesophageal varices using transient elastography is disease specific. J Viral Hepat 2011; 18: e75e80.

24- Bureau C, Metivier S, Peron JM, et al. Transient elastography accurately predicts presence of significant portal hypertension in patients with chronic liver disease. Aliment PharmacolTher 2008; 27: 1261-1268.

25- Malik R, Lai M, Sadiq A, et al. Comparison of transient elastography, serum markers and clinical signs for the diagnosis of compensated cirrhosis. J GastroenterolHepatol 2010; 25: 15621568.

26- Nguyen-Khac E, Saint-Leger P, Tramier B, Coevoet H, Capron D, Dupas JL. Noninvasive diagnosis of large esophageal varices by fibroscan: strong influence of the cirrhosis etiology. Alcohol ClinExp Res 2010; 34: 11461153.

27-Bintintan A, Chira RI, Bintintan VV, Nagy GA, Manzat-Saplacan MR, Lupsor-Platon M, Stefanescu H, Duma MM, Valean SD, Mircea PA. Value of hepatic elastography and Doppler indexes for predictions of esophageal varices in liver cirrhosis. Med Ultrason 2015; 17: 5-11.

28- Hashish M, Ragab M, Mahmoud H. Liver Stiffness Measurment By Fibroscan For Predicting The Grades Of Oesophageal Varices In HCV Cirrhotic Patients. Journal of Environmental Science. 2019;45(3):49-68.

29- Hassan E, Omran D, El Beshlawey M, Abdo M, El Askary A. Can transient elastography, Fib-4, Forns Index, and Lok Score predict esophageal varices in HCV-related cirrhotic patients?. Gastroenterología y Hepatología. 2014;37(2):58-65.

30-Madhotra R, Mulcahy HE, Willner I, Reuben A. Prediction of esophageal varices in patients with cirrhosis. J ClinGastroenterol. 2002; 34:8185.

31-Pinzani M, Vizzutti F, Arena U, Marra F. Technology Insight: noninvasive assessment of liver fibrosis by biochemical scores and elastography. Nat ClinPractGastroenterolHepatol 2008; 5:95-106.

32-Badawi R, Wasfy E, ElKassas G et al. A Novel Non-invasive Score Precisely Predicts Development of Esophageal Varices in Patients with Chronic Viral Hepatitis C. Govaresh 2020;25:56-64.

33-Castera L, Sebastiani G, Le Bail B, de Ledinghen V, Couzigou P, Alberti A. Prospective comparison of two algorithms combining non-invasive methods for staging liver fibrosis in chronic hepatitis C. J Hepatol 2010; 52:191-198.