

Liver Stiffness Measurement by Fibroscan Predicts the Presence and Size of Esophageal Varices in Egyptian Patients with HCV Related Liver Cirrhosis

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ABSTRACT

Background and Aim: Liver stiffness measured by transient elastography correlates with Hepatic vein pressure gradient, liver Stiffness value of 21 kpa predicts significant portal hypertension. Aim is to predict esophageal varices presence by fibroscan and possible grading by degree of liver stiffness in HCV related cirrhotic patients.

Material and Methods: Thirty two HCV related cirrhotic patients were recruited, age > 18 years, BMI < 35, no history of: upper GI bleeding, hepatocellular carcinoma, abdominal collaterals, ascites. Patients underwent clinical examination, laboratory investigations, abdominal ultrasonography, upper endoscopy and fibroscan. They divided into (Group I= no varices, Group II =small varices (Grade 1 & 2), Group III = large varices (Grade 3 & 4).

Results: Age is higher in Group III than I & II (55+6.6 vs 49.5+4.7 & 48.9+4.7, p-value 0.04) respectively, Groups were gender & BMI matched, fibroscan values in Group I vs II & III were 27 Vs 49.4, p value 0.01, cutoff 29.7 Kpa (sensitivity 95% & specificity 67%) while its value in Group II vs III were 38.4 vs 60.4, p value 0.002, cutoff 38.2 Kpa (sensitivity 100% & specificity 77.3%). Platelet count, splenic size, platelet count/splenic size in Group I vs II & III were 107.166 vs 72.900, 13.8 vs 15.4, 803.6 vs 478, p value 0.01, 0.008, 0.005, cutoff 80.000, 14.5, 545, sensitivity & specificity (85%&75%, 75%&75%, 85%&84%) respectively. On multivariate analysis fibroscan (OR 1.113; p=0.005) & platelet count/splenic size (OR 0.995; p=0.012) were positive predictors of esophageal varices presence.

Conclusion: Fibroscan is a good non-invasive method to predict esophageal varices presence & possible grading with high sensitivity.

Key words: Fibroscan, Esophageal varices, Grading, Non-invasive methods

INTRODUCTION

Cirrhosis is a consequence of almost all progressive chronic liver diseases, approximately 10%-20% of patients with chronic hepatitis C virus infection have cirrhosis at first clinical presentation, and as many as 20%-30% of those who don't have cirrhosis will eventually develop this condition and its complications within one or more decades [1]. Development of oesophageal varices is a major complication that may occur in up to 90% of cirrhotic patients [2]. Esophageal varices may lead to variceal bleeding that is a life threatening event that has an incidence of 5% in patients with small oesophageal varices and upto 15% in those with large esophageal varices. Mortality per bleeding episode is around 10%-20% [3]. Therefore, screening for esophageal varices in cirrhotic patients is a strong recommendation in all consensus statement [4].

The current screening method is endoscopy at 2-3 years in patients without esophageal varices and at 1-2 years in those with small varices, this approach is invasive. That is why selection of patients with large esophageal varices at high risk for bleeding has become an issue of growing importance.

In this respect, several clinical, biological, ultrasonographic and elastographic (transient elastography-TE) methods have been proposed (and some of them were validated) as non-invasive alternatives to endoscopy [5]. This work was designed to study the validity of liver stiffness measurement by fibroscan to predict the presence of esophageal varices in cirrhotic patients due to

hepatitis C virus infection (Primary aim) and to determine the grade of esophageal varices by the degree of liver stiffness measured by fibroscan.

PATIENTS AND METHODS

I. Patients

This study was performed on 32 patients in the period from April 2011 to October 2011. Diagnosis of liver cirrhosis was based on history, clinical, laboratory and radiological data. All patients fulfilled the following criteria:

Inclusion criteria: 1- Adult patients ≥ 18 years, 2-Hepatitis C virus infection, 3- Liver cirrhosis without moderate or massive ascites, mild pelvic ascites could be recruited, 4- no history of upper GI bleeding or hepatocellular carcinoma and 5- BMI <35.

Exclusion criteria for the recruited patients: 1- Patients age <18 years, Other causes of liver cirrhosis except HCV, 2- BMI > 35, 3- Liver cirrhosis with moderate or massive ascites, 4- History of upper GI bleeding or hepatocellular carcinoma, 5-Patients with abdominal collaterals in abdominal ultrasound.

Patients were classified into three Groups: Group I: included patients with liver cirrhosis and without esophageal varices. Group II: included patients with liver cirrhosis and small esophageal varices (Grade I&II). Group III: included patients with liver cirrhosis and large esophageal varices (Grade III & IV).

II. Methods

After getting a written consent from all patients, they were asked to undergo the following:

1. Full history taking with special emphasis on previous history of schistosomiasis, history of viral hepatitis or exposure to risk factors (such as anti-schistosomiasis injections, blood transfusion or previous surgical operations), history of jaundice, disturbed conscious level, bleeding tendency, hematemesis or melena.
2. Full clinical examination for stigmata of liver cell failure or signs of portal hypertension were obtained.

III. Laboratory investigations included

Complete blood count, serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), total and direct bilirubin, serum albumin, prothrombin time and concentration, Alphafeto protein and HCV Ab.

IV. Abdominal ultrasonography

Using real time scanning device Toshiba, Aplio MX with convex probe, 3-5uHz to detect the presence of liver cirrhosis(irregular surface, coarse texture, attenuated hepatic veins),Signs of portal hypertension (presence of abdominal collaterals, splenomegaly), ascites and to exclude hepatic focal lesion.

V. Upper Gastrointestinal Endoscopy

Using Olympus GIF 160-Q165 (EXERA II), to evaluate the presence and degree of varices in addition to any relevant upper GIT lesions.

Classification of oesophageal varices was done according to Thakeb classification (1988):

Grade 1: Small straight cords of varices confined to the lower third of esophagus.

Grade 2: Moderate sized clubbed varices, with well defined areas of normal mucosa between them, forming several distinct variceal cords and confined to the lower half of the esophagus.

Grade 3: Gross varices extending into the proximal half of the esophagus, normal mucosa might not be visible in between them unless the esophagus is fully distended with air.

Grade 4: Varices like those of grade 3 but with dilated capillaries on top or in between them and encroaching on esophageal lumen.

VI. Liver stiffness measurement (LSM)

Using Fibroscan that was performed within days following or preceding upper GI tract endoscopy, the operators were not aware of the results of endoscopy.

Interpretation of results of Fibroscan

1. Up to ten successful acquisitions were performed on each patient. Success rate was calculated as the ratio of the number of successful acquisitions over the total number of acquisitions.
2. The median value of successful measurements was kept as representative of the liver stiffness.
3. Only LSM obtained with 10 successful acquisitions and a success rate of at least 60% was considered reliable [6].

The following table shows the relation between Fibroscan reading in K Pascal and the stage of fibrosis [7].

STATISTICAL ANALYSIS

Data were statistically described in terms of mean ± standard deviation (± SD), median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study Groups was done using Mann Whitney U test for independent samples when comparing

F0	0 : 2.9
F1	3 : 5.9
F2	6 : 8.9
F3	9 : 16.9
F4	17 : 75

2 Groups and Kruskal Wallis test with posthoc multiple 2-Group comparisons when comparing more than 2 Groups. For comparing categorical data, Chi-square (c2) test was performed. Exact test was used instead when the expected frequency is less than [5]. Accuracy was represented using the terms sensitivity and specificity. Receiver operator characteristic (ROC) analysis was used to determine the optimum cut off value for the studied diagnostic markers. Univariate and multivariate regression models were constructed to determine the significant independent predictors for the occurrence of OV, the grade of OV and occurrence of large OV. p values less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

RESULTS:

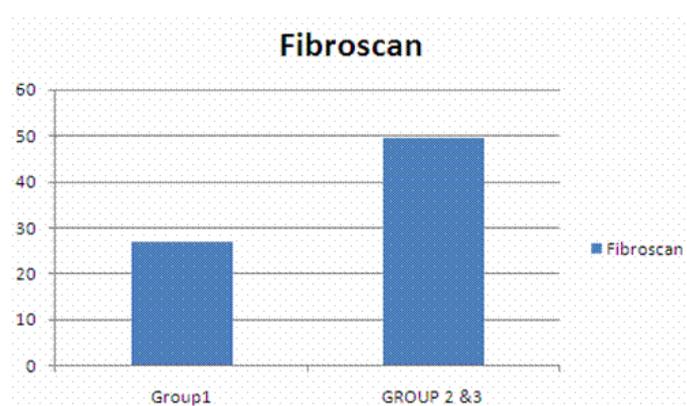
The demographic data of the studied Groups were shown in [Table/Fig-1], age was significantly higher in Group III compared to Group I and II (55+6.6 vs 49.5+4.7 and 48.9+4.7, p-value 0.04) respectively, while gender and BMI were matched in studied Groups, the modified Child-Pugh and MELD scoring were shown in [Table/Fig-2].

Numbers	Group I n=12	Group II n=10	Group III n=10	p-value
Age (years)	n=12	n=10	Group III	0.04
Gender M/F	n=10	n=10	p-value	0.05
BMI (Kg/m ²)	n=10	p-value	27.3+4.7	0.6
CP A/B	12/0	8/2	3/7	0.001
MELD score	9.1	8.8	14	0.004
Hb (gm/ml)	12.8±1	13.2±1	10.7±2	0.002
TLC/ccm	4.8±1.2	5±1.6	3.5±9.7	0.048
Platelets/ccm	107.1±53	80.7±16	65.1±10.8	0.01
ALT(IU/L)	46.5±21	59.8±27	48.2±22.8	0.06
AST(IU/L)	56.5±23	69.4±28	67.2±29.8	0.6
T. bilirubin (mg/dl)	0.95±0.4	1.4±0.7	1.9±1	0.03
S. albumin (mg/dl)	3.7±0.4	3.5±0.2	3.2±0.3	0.01
INR	1.2±0.2	1.5±0.1	1.6±0.3	0.01
AFP	21.3±17	23.1±27	18.4±14	0.9

[Table/Fig-1]: Characteristics of studied patients

*p < 0.05 is significant

Data are reported as mean +SD except in CPS that represented as number of patients. BMI, body mass index; AST, CP, Child Pugh; MELD, model of end stage liver disease; Hb, hemoglobin; TLC, total leukocyte count; ALT, alanine aminotransferase; aspartate aminotransferase; S. Albumin, serum albumin; AFP, alpha feto protein.



[Table/Fig-2]: Comparison between groups.

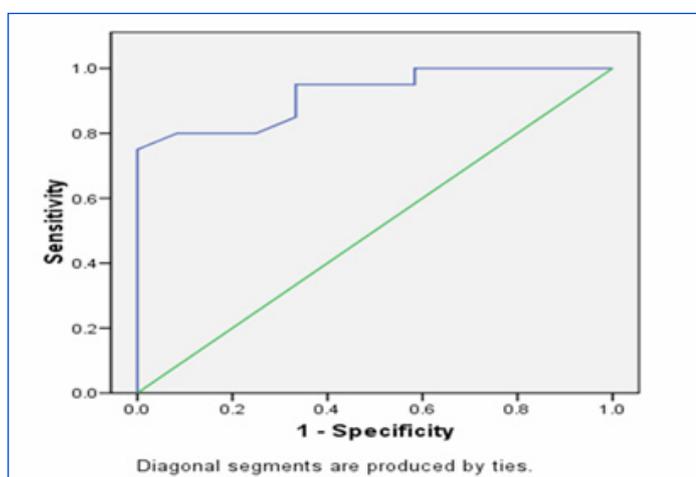
Laboratory parameters; hemoglobin level, white blood cell count, platelet count & serum albumin were significantly lower and total bilirubin, and INR level were higher in Group III than in other Groups denoting severity of liver disease in this Group while studied Groups were matched as regard ALT, AST and Alpha fetoprotein.

Mean liver stiffness value measured by fibroscan was significantly higher in Group II & III compared with Group I (49.4 Kpa Vs 27 Kpa, respectively, $p = 0.01$), shown in [Table/Fig-3] and [Table/Fig-4]. Cutoff value for prediction of varices was 29.7 Kpa

O.V	No.	Mean Liver stiffness value (Kpa)	p Value
No varices (Group I)	12	27	0.01
Presence of varices (Group II, III)	20	49.4	
Small Varices (Group II)	10	38.4	0.002
Large Varices (Group III)	10	60.4	

OV: esophageal varices

[Table/Fig-3]: Correlation between Liver stiffness values and prediction of presence and size of O.V

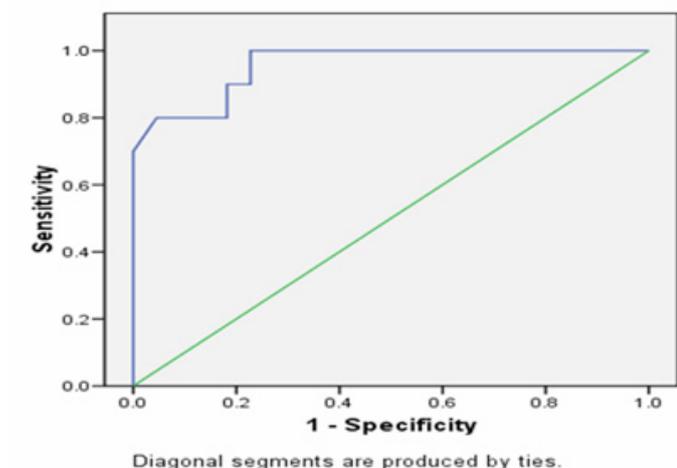


[Table/Fig-4]: ROC curve Correlation between Liver stiffness values and prediction of presence and size of O.V

	Cut-off value	Sensitivity	Specificity
For prediction of Presence of OV	29.7 Kpa	95%	67%
For prediction of large OV	38.2 Kpa	100%	77.3%

OV: esophageal varices.

[Table/Fig-5]: The cut-off values of liver stiffness for studied patients



[Table/Fig-6]: ROC Curve the cut-off values of liver stiffness for studied patients

(sensitivity 95% and specificity 67%), shown in [Table/Fig-5] & [Table/Fig-6]. Mean liver stiffness value in Group III (large varices) was significantly higher compared with Group II (small varices) (60.4 Kpa Vs 38.4 Kpa respectively, $p = 0.002$) and cut off value of liver stiffness measured by fibroscan for prediction of large varices was 38.2 Kpa (sensitivity 100% and specificity 77.3%), shown in [Table/Fig-6] and [Table/Fig-7]. When we studied other non-invasive methods for prediction of esophageal varices we found platelets count, splenic size and platelets count/splenic size ratio were significantly correlated with the presence of esophageal varices (p value = 0.01, 0.008 & 0.005 respectively) shown in [Table/Fig-8]. Cut off values for platelets count, splenic size and platelets/splenic size ratio for prediction of esophageal varices were 80000, 14.5 cm & 545 respectively, while prediction of large varices were possible at platelets count 69000 as a cut off value & platelets/splenic size ratio at 472, shown in [Table/Fig-9]. When

O.V	No.	Platelets counts	Splenic size	Plt/Splenic size ratio
No varices (Group I)	12	107.166	13.8	803.6
Presence of varices (Group II, III)	20	72.900	15.4	478
P Value		0.01	0.008	0.005

[Table/Fig-7]: Prediction of esophageal varices by non-invasive parameters other than liver stiffness:

O.V	Platelets counts	Splenic size	Plt/Splenic size ratio
Cut off value for presence of varices	80.000	14.5	545
Sensitivity	85%	75%	85%
Specificity	75%	75%	84%
Cut off value for presence of large varices	69.500		472
Sensitivity	80%		90%
Specificity	90%		80%

OV: esophageal varices.

[Table/Fig-8]: Cutoff values of non-invasive parameters other than liver stiffness for prediction of esophageal varices.

	p-value	OR	95 %CI for OR	
			Upper	Lower
Liver stiffness	0.005	1.113	1.199	1.033
Platelet count/Spleen Size ratio	0.012	0.995	0.999	0.991

[Table/Fig-9]: Liver stiffness by Fibroscan versus Platelet count/Spleen size ratio for prediction of esophageal varices.

we compared liver stiffness measured by fibroscan versus other non-invasive methods, namely platelets count, splenic size and platelets/splenic size ratio, only liver stiffness and platelets/splenic size ratio in a multivariate analysis were found significantly capable to predict presence of esophageal varices (p value = 0.005 & 0.02 respectively, OR was 1.113 & 0.995 respectively, shown in.

DISCUSSION

Bleeding from esophago-gastric varices is the most important complication of cirrhosis [8]. The first crucial step in prevention is to identify the patients at risk for bleeding by endoscopic screening, in order to select them for prophylactic treatment [9]. Since a variable proportion of patients will not have varices; thus, screening all cirrhotic patients with upper GI endoscopy implies a number of unnecessary endoscopies, which increase the workload

of endoscopy units. In addition, compliance with endoscopic screening recommendations may be limited [10].

Predicting the presence of esophageal varices by non-invasive means would permit to restrict the performance of endoscopy to those patients with a high probability of having varices [11].

The aim of this study was to predict the presence of esophageal varices by measurement of liver stiffness by fibroscan in cirrhotic patients due to hepatitis C virus infection and to determine the grade of esophageal varices by the degree of liver stiffness.

In the present study Child Pugh score was statistically significant higher in patients with esophageal varices (Groups II-III) than those without esophageal varices (Group I) and this is in agreement with [12] who found a significant relation between presence of varices and increased Child score. Thus, the more advanced the liver disease the more likely the presence of varices.

In the present study, platelet count was significantly lower in patients with esophageal varices-Group II (mean= 80700) & III (mean= 65100), than in patients without esophageal varices-Group I (mean =107166), p value = 0.01. Platelet count may decrease for several reasons in patients with chronic liver disease. Madthora et al. [12] reported that 32% of the studied cirrhotic patients had platelet count less than 68000/mm³ without detectable splenomegaly; this might be explained by the insufficient synthesis of thrombopoietin. Other potential explanations for this phenomenon are presence of antithrombotic antibodies and thrombocyte associated immunoglobulin, which can be found in the sera of patients with liver diseases [13]. Thus the use of platelet count alone as a non-invasive predictor of esophageal varices can be misleading and cannot be solely attributed to portal hypertension. Indeed, the use of the platelet count/spleen diameter ratio bypasses this possible drawback since it "normalizes" platelet count to splenic sequestration [14].

As regard spleen size, we found that it was statistically significantly higher in patients with esophageal varices-Group II & III (mean = 15.4) than those without esophageal varices-Group I (mean = 13.87), p value = 0.008, so measurement of splenic size by ultrasonography is considered a non-invasive predictive indicator of the development of gastro-esophageal varices in liver cirrhosis [15].

In the present study; platelet count/spleen size ratio was significantly lower in patients with esophageal varices (mean= 478.80) than patients without (mean= 803.67) and at the best cut-off value of 545 (sensitivity 85% and specificity 84%). Other studies document higher cutoff with more specificity and sensitivity. Agha et al., [16] reported cut off value 909 with 100 % sensitivity, 97.6 % specificity and Giannini et al., [17] reported the same cutoff value 909 with 91.5 % sensitivity, 67.0 % specificity. This difference in the results could be attributed to the lower sample size. Moreover Chawla et al., [18] stated that platelet count/spleen size ratio may not be adequate to completely replace esophagogastroduodenoscopy as a non-invasive screening tool for the presence of esophageal varices.

In this study liver stiffness measurement was significantly higher in patients with esophageal varices (Groups II & III) than those with no varices (Group I); at the best cut off value 29.7KPa, liver stiffness measurement sensitivity was 95 % and specificity was 67 %. Also, it was significantly higher in patients with large varices (Group III) than in patients with small varices (Group II); at the best cut off value 38.2KPa liver stiffness measurement sensitivity was 100 % and specificity was 77.3 %.

In agreement with our results Sporea I et al., [19] studied 1000 patients with TE and showed more or less equivalent cut off values (For the presence of varices, the optimal Fibroscan cut-off was 31 kPa and for bleeding cut-off was 50.7 KPa), according to Lebrec [20]; the larger the size of varices the higher risk of bleeding and

according to Sporea [19] study cut off value for TE to predict risk of bleeding could be considered as cut off value for prediction of large varices. Moreover, studies carried out by Vizzutti et al., [21] a cut-off value for prediction of varices was 17.6 kPa, these cut off values are smaller than we obtained, but the different demographics and patients characteristics as well as the type of fibroscan machines could be the reason for these discrepancy. More over Castera L et al., [22] showed that Transient elastography could be a valuable tool in diagnosis of cirrhosis but cannot replace endoscopy for variceal screening.

On multivariate analysis of other non-invasive parameters for the detection of presence of varices in our results, the fibroscan has the highest significant value followed by platelets count/ splenic size which confirm the previous study carried by Kazemi et al., [23]. Accordingly, liver stiffness measurement by fibroscan is suggested as a simple non-invasive physical parameter, allows identifying among patients with well-compensated cirrhosis a large Group ineligible for variceal screening as having a low probability of bearing varices and particularly large varices, limiting therefore the indications of endoscopic screening.

According to our knowledge, there are no available reports about the use of non-invasive methods to predict the grading of esophageal varices. The available studies were only capable of predicting the development of varices and may be the possibility of prediction of varices with high risk of bleeding. Our pilot study is the first study that showed the capability of prediction of grading of esophageal varices and could pave the way to larger studies to confirm our data. The use of fibroscan in the prediction as well as grading of esophageal varices could be very helpful on planning for the management of cirrhotic patients to prevent the morbidity and mortality developing from bleeding varices.

In conclusion; Liver stiffness measurement by fibroscan is valuable in predicting the presence of esophageal varices in patients with liver cirrhosis and of higher diagnostic value than other non-invasive parameters in predicting the size of esophageal varices. It may help to select patients for endoscopic screening.

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