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Original Article

Relationship between Liver Stiffness Measured by Fibroscan and the Presence and Grading of Esophageal Varices by Endoscopy in Patients with Liver Cirrhosis

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Abstract:

Background: Fibroscan (transient elastography) is a relatively new method of measuring liver stiffness and is a noninvasive liver fibrosis marker. The liver stiffness could be used as predictors of oesophageal varices in cirrhotic patients because portal hypertension is related to liver fibrosis.

Objectives: This study aimed to evaluate the diagnostic accuracy of transient elastography for the presence and grade of oesophageal varices (EV) in patients with liver cirrhosis.

Methods: This cross-sectional study was conducted in the Department of Medicine and Department of Gastroenterology Sylhet MAG Osmani Medical College Hospital, Sylhet between July 2018 and June 2019. Seventy two consecutive cirrhotic patients (mean age 47.21 ± 14.02 years, 73.6% males) were enrolled. Patients with hepatocellular carcinoma, liver cirrhosis with moderate or massive ascites, acute liver failure, previous variceal bleeding, treatment with ß blockers, sclerotherapy or band ligation of oesophageal varices, transjugular intrahepatic portosystemic shunt or surgery for portal hypertension, liver transplantation, portal, splenic or hepatic vein thrombosis revealed by the abdominal ultrasonography, Spontaneous bacterial peritonitis, extrahepatic cholestatsis, congestive cardia failure, BMI 30 or above were excluded . All patients underwent fibroscan (transient elastography) and upper GI endoscopy. The diagnostic performance of the methods was assessed using sensitivity, specificity, positive predictive value, negative predictive value, accuracy and receiver operating characteristic curves.

Results: Oesophageal varices were found in 86.1% with grade-I in 22.2%, Grade-II in 31.9%, Grade-III in 31.9% and no oesophageal varices 13.9% of patients. A significant positive correlation revealed between liver stiffness measured by fibroscan and presence ($r=0.568$; $p<0.001$) and grade ($r=0.783$; $p<0.001$) of oesophageal varices. The best cutoff value of liver stiffness measurement was 14.45 kPa in predicting the presence of oesophageal varices with the sensitivity of 98.4%, specificity of 90.0%, positive predictive value (PPV) of 98.4%, negative predictive value (NPV) of 90% and area under the curve (AUROC) of 0.967; and 41.55 kPa for large oesophageal varices (grade-II and III) with the sensitivity 95.7%, specificity 92.3%, PPV 95.7%, NPV 92.3% and AUROC 0.965.

Conclusion: Liver stiffness measurement by fibroscan is correlated with presence and grading of oesophageal varices in liver cirrhosis. Measurement of liver stiffness by fibroscan is reliable for predicting the presence and larger grade of oesophageal varices by endoscopy in patients with liver cirrhosis. Therefore, it is a good test to replace endoscopy for predicting and grading of oesophageal varices.

Keywords: Fibroscan, transient elastography, oesophageal varices, liver stiffness, AUROC (area under operating characteristic curve).

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Introduction:

Liver cirrhosis is the end stage of every chronic liver disease, resulting in formation of fibrous tissue, disorganization of liver architecture, and nodule formation, which interferes with liver function and results in portal hypertension.[1]

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Portal hypertension is associated with development of a hyperdynamic circulation and complications such as ascites, hepatic encephalopathy, and oesophago-gastric varices.[2]

Development of oesophageal varices is a major complication that may present at diagnosis in approximately 50% of cirrhotic patients, being more common in Child-Pugh class C patients

compared to Child-Pugh class A patients (85% versus 40%). De novo formation of varices occurs at a rate of 5% per year in patients with liver cirrhosis. Once varices form, they enlarge from small to large at a rate of 5–12% per year.[1]

Oesophageal 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 up to 15% in those with large oesophageal varices.[3] The risk of bleeding of 25-35% in a year has been detected. The mortality rate of each bleeding episode is 17-57% and almost 70% patients without treatment died within 1 year of their first bleeding.[4]

Early diagnosis of varices before the first bleed is essential as studies of primary prophylaxis using non-selective beta blockers and endoscopic variceal ligation clearly show that the risk of variceal haemorrhage can be reduced by 50% to about 15% for large oesophageal varices,1 and has been shown to be an effective prophylaxis, particularly against the first variceal bleeding.[4,5] Therefore, screening for oesophageal varices in cirrhotic patients to detect high risk patients is a strong recommendation in all consensus statement.[2,6]

The recommendation is that all cirrhotic patients should be screened for varices at diagnosis, with follow up every 2-3 years for patients without varices (depending upon liver disease severity) and 1-2 years for patients with small varices, to assess for enlargement of varices and need for prophylactic treatment.[7,8]

Upper GI endoscopy is the gold standard to detect oesophageal varices. However, a generalized screening program of periodic upper gastro-intestinal eendoscopy in cirrhotic patients may lead to low compliance since endoscopy is an unpleasant, uncomfortable, invasive and costly procedure.[9]

Therefore, some non-invasive parameters for predicting the presence and the degree of oesophageal varices in patients with liver cirrhosis, which are the biochemical, clinical, ultrasonographic and elastrographic (Fibroscan) methods have been proposed (and some of them will be validated) as non-invasive alternatives to endoscopy.[6,10]

Liver stiffness measurement (LSM) is an elastometric technique that uses the principle of vibration controlled transient elastography to assess tissue elasticity. LSM is expressed in kilopascals (kPa). Normal transient elastography values are considered to be 3.8–8 kPa in men and 3.3–7.8 kPa in women. A value of 13 kPa or above indicates cirrhosis.[11,12] In chronic liver disease patients it was proved to be a very useful tool to assess significant fibrosis and to rule out cirrhosis.

Based on the concept that the development of portal hypertension is due to liver fibrosis, transient elastography (Fibroscan) has been tested as predictors of oesophageal varices in cirrhotic patients with promising results, which is painless, rapid, and easy to perform.[1]

For the diagnosis of variceal presence, area under the receiver operating characteristic curve (AUROC) curves varied from 0.76–0.85, with a sensitivity of 84–95%, specificity of 43–78%, positive predictive value (PPV) 57–89%, and negative predictive value (NPV) 66–91% using cut-offs between 13.9–21.5 kPa. For the diagnosis of large oesophageal varices, AUROC varied from 0.76–0.87, with sensitivities of 77–91%, specificities of 60–85%, PPV 48–56% and NPV 94-95% using cut-offs between 19–30.5 kPa.[12-16]. So, this study is designed to evaluate role of liver stiffness measurement by fibroscan to predict the presence and size of oesophageal varices in liver cirrhosis.

Objectives of the study

General: To evaluate the role of liver stiffness measurement by fibroscan to predict presence and severity of oesophageal varices in liver cirrhosis.

Specific: To achieve the above mentioned general objective, the specific objectives were

- To record liver stiffness measurement by fibroscan in patients with liver cirrhosis.

- To record endoscopic findings of upper gastrointestinal tract and to determine the presence and grade of oesophageal varices in patients with liver cirrhosis.
- To compare the different values of liver stiffness measurement with presence and grade of oesophageal varices in liver cirrhosis.

Materials and Methods:
This cross-sectional study was conducted in the Department of Medicine Sylhet MAG Osmani Medical College Hospital, Sylhet, Bangladesh during the period from July 2018 to June 2019 with a view to find the role of liver stiffness measurement by fibroscan to predictct presence and severity of oesophageal varices in liver cirrhosis. A diagnostic work up was made by stigmata of cirrhosis, abdominal ultasonogram and liver function tests for all patients.72 consecutive cirrhotic patients were enrolled after fullfilling the criteria. All patients underwent fibroscan (transient elastography) and upper GI endoscopy. The diagnostic performance of the methods was assessed using sensitivity, specificity, positive predictive value, negative predictive value, accuracy and receiver operating characteristic curves. Statistical analyses of the results were obtained by using windows-based computer software Statistical Packages for Social Sciences (SPSS-22).

Results: The outcome of the study was as follows:

Table-1: Age distribution of the patients (n=72)

Age	Frequency	Percentage
21-30 years	12	16.7
31-40 years	11	15.3
41-50 years	20	27.8
51-60 years	14	19.4
61-70 years	15	20.8
Mean	47.21 ± 14.02	21-70

Table-2: Distribution of patients according to sex (n=72)

Sex	Frequency	Percentage
Male	53	73.6
Female	19	26.4
Total	72	100.0

Table-3: Distribution of respondents according to viral marker (n=72)

Viral marker	Frequency	Percentage
Hepatitis B virus	35	48.6
Hepatitis C virus	3	4.2
Alcholic	3	4.2
NASH	10	13.9
Unknown	21	29.2
Total	72	100.0

Table-4: Distribution of patients according to presence or absence of oesophageal varices (n=72)

Varices	Frequency	Percentage
Present	62	86.1
Absent	10	13.9
Total	72	100.0

Table-5: Distribution of patients according to grade of oesophageal varices (n=72)

Oesophageal varices	Frequency	Percent
Grade-I (Mild)	16	22.2
Grade-II (Moderate)	23	31.9
Grade-III (Severe)	23	31.9
Absent	10	13.9
Total	72	100.0

Table-6: Comparison of liver stiffness measurements between presence and absence of oesophageal varices (n=72)

LSM in kPa	Oesophageal varices		*p-value
	Present (n=62	Absent (n=10)	
Mean±SD	54.57±20.76	16.36±7.90	P<0.001
Range	13.90-75.00	13.10-38.80	

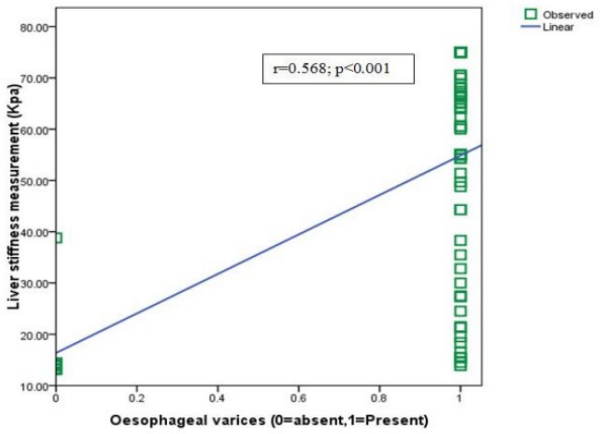
Table-7: Comparison of liver stiffness measurements among different grade of oesophageal varices (n=72)

LSM in kPa	Oesophageal varices				*p-value
	Absent	Grade-I	Grade-II	Grade-III	
Mean ± SD	16.36 ± 7.90	27.94 ± 15.04	63.46 ± 8.82	65.00 ± 15.85	p<0.001
Range	13.10-38.8	13.90-38.30	44.30-75.00	27.5-75.00	

Table-8: Comparison of liver stiffness measurements between absence or small oesophageal varices and large varices (n=72)

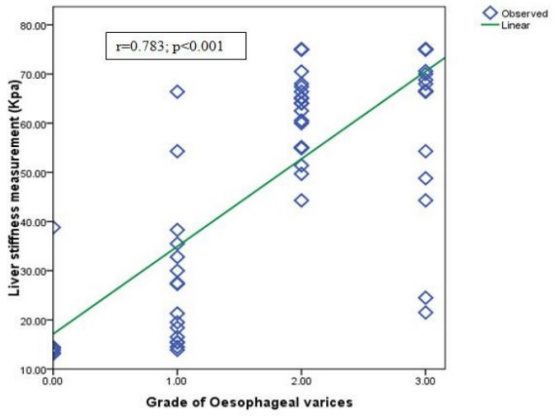
LSM in kPa	No or small varices (n=26)	Large varices (n=46)	*p-value
Mean ± SD	23.49 ± 13.83	64.23 ± 12.70	P<0.001
Range	13.10-66.4	21.50-75.00	

Figure-1: Correlation between Transient Elastography and presence of oesophageal varices (n=72)



* Pearson correlation was used to analyse the data. Transient elastography measures (liver stiffness measurement) showed a significant positive correlation with the presence of oesophageal varices (r=0.568; p<0.001).

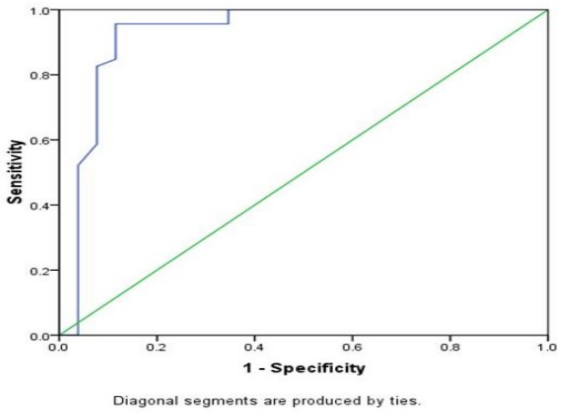
Figure-2: Correlation between Transient Elastography and grade of oesophageal varices (n=72).



*Pearson correlation was used to analyse the data. 0=No, 1=Grade-I, 2=Grade-II and 3=Grade-III oesophageal varices Transient elastography measures (liver stiffness measurement) showed a positive correlation with the grade of oesophageal varices (r=0.783; p<0.001).

Table-9: Cross tabulation of the liver stiffness measurement at cut-off value of ≥14.45 kPa in predicting oesophageal varices (n=72)

Liver stiffness measurement	Oesophageal varices		Total
	Present	Absent	
≥ 14.45 kPa	61 (TP)	1 (FP)	62
<14.45 kPa	1 (FN)	9 (TN)	10
Total	62	10	



Receiver-operating characteristic curve of liver stiffness measurement for the diagnosis of criterion 'oesophageal varices grade II or III' versus 'oesophageal varices grade I or none'. AUROC = 0.965;

Discussion:

The present study findings were discussed and compared with previously published relevant studies.

Variceal bleeding is a major complication of cirrhosis, associated with a hospital mortality rate of 10%– 20%.The prevalence of varices in patients with cirrhosis is approximately 60-80% and the risk of bleeding is 25-35%. Prevention of oesophageal variceal bleeding remains at the forefront of longterm management of cirrhotic patients. The most reliable and accurate method to detect the presence of large oesophageal varices is an upper gastrointestinal endoscopy.

It is now recommended that all patients with established cirrhosis should be screened by upper gastrointestinal endoscopy for the presence of varices at the time of diagnosis and patients without varices or with small varices should be re-endoscoped every 1–3 years.[17] However, less than 50% of cirrhotic patients have varices at the screening endoscopy and the

majorities have small-sized varices, which carry a very low risk of bleeding.

Also a substantial number of patients will not develop large varices during screening and therefore will undergo unnecessary endoscopies which are uncomfortable, invasive, and costly. Over the years, a great effort has been made either to introduce less invasive, alternative to standard endoscopy diagnostic methods or to restrict the performance of endoscopy in high-risk patients by using a variety of noninvasive predictors.[18]

In this study oesophageal varices were present in 86.1% of patients and 13.9% of patients had no oesophageal varices. Grade-I (Mild) oesophageal varices were found in 22.2% of patients, Grade-II (Moderate) oesophageal varices were in 31.9% of patients and Grade-III (Severe) oesophageal varices were in 31.9% of patients. No oesophageal varices were in 13.9% of patients.

This study showed liver stiffness measurements (kPa) was 54.57 ± 20.76 in patients with presence of oesophageal varices and was 16.36 ± 7.90 in patients with absence of oesophageal varices. Liver stiffness measurements was significantly higher in those with presence of oesophageal varices compared to those without oesophageal varices ($p<0.001$). Sarkar et al.[19] demonstrated liver stiffness measurements was 34.57 ± 20.00 kPa patients with presence of oesophageal varices and was 13.32 ± 10.63 kPa in patients without oesophageal varices; difference was significant ($p<0.001$). Hassan et al.[20] found liver stiffness measurements was 30.830 ± 13.969 kPa in those with presence of oesophageal varices and was 18.900 ± 2.877 kPa in those without oesophageal varices. Liver stiffness measurements was significantly higher in those with presence of oesophageal varices compared to those with absence of oesophageal varices ($p<0.001$).

This study showed liver stiffness measurements (LSM) was 16.36 ± 7.90 kPa in patients with absence of oesophageal varices, 27.94 ± 15.04 kPa in those with grade-I oesophageal varices, 63.46 ± 8.82 kPa in patients with grade-II oesophageal varices, was 65.00 ± 15.85 kPa in patients with grade-III oesophageal varices. There was a significant difference of liver stiffness measurements among different degree of oesophageal varices ($p<0.001$).

Post Hoc analysis revealed significantly higher LSM in grade 1, grade 2 and grade 3 oesophageal varices compared to no oesophageal varices ($p=0.123$; $p<0.001$, $p<0.001$) respectively. Hu et al.[21] found that liver stiffness measurements were a significant difference of liver stiffness measurements among different degree of oesophageal varices. Liver stiffness measurements was significantly higher in large oesophageal varices compared to no oesophageal varices ($p<0.001$).

In this study liver stiffness measurement showed a significant positive correlation with the presence of oesophageal varices ($r=0.568$; $p<0.001$) Vizzutti et al.[14] reported that LSM positively correlated with the presence of OV.

In the present study transient elastography measures of LSM showed a significant positive correlation with the grade of oesophageal varices ($r=0.783$; $p<0.001$).

In this study at cut-off value ≥14.45 kPa of liver stiffness measurement can predict presence of oesophageal varices with the sensitivity of 98.4%, specificity of 90.0%, positive predictive value (PPV) of 98.4%, negative predictive value (NPV) of 90% and AUROC of 0.967.

This study revealed that large oesophageal varices (grade-II and III) detection by liver stiffness measurement at cut-off value of ≥ 41.55 kPa, the sensitivity was 95.7%, specificity was 92.3%, PPV was 92.3%, NPV was 92.3% and AUROC was 0.965. Hassan et al.[20] found large oesophageal varices (grade-II and III) detection by liver stiffness measurement at cut-off value of ≥ 22.2 kPa, the sensitivity was 84%, specificity was 72%, positive predictive value (PPV) was 84%, negative predictive value (NPV) was 72% and accuracy was 80%.

Conclusion:

In conclusion, liver stiffness measurement by fibroscan is correlated with presence and grading of oesophageal varices in liver cirrhosis. Measurement of liver stiffness by fibroscan is reliable for predicting the presence and larger grade of oesophageal varices by endoscopy in patients with liver cirrhosis. Therefore, it is a good test to replace endoscopy for predicting and grading oesophageal varices.

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