THE VALUE OF FIBROSCAN IN PREDICTION OF VARICEAL BLEEDING RISK

Iulia Ratiu

REZUMAT

Introducere: Elastografia impulsională (Fibroscan) este o metodă noninvazivă care poate evalua severitatea fibrozei hepatice la pacienții cu hepatopatii cronice. **Obiectiv:** Scopul acestui studiu a fost evaluarea valorii elastografiei în predicția hemoragiei variceale. **Material și metode:** Am evaluat retrospectiv 149 de pacienți cu ciroză hepatică, împărțiți în 2 loturi: lotul A cu hemoragie variceală (72 cazuri) și lotul B fără sângerare (77 cazuri). Am comparat valorile obținute la FibroScan între cele două grupuri, utilizând testul t- nepereche și am stabilit o valoare de cut-off pentru riscul de hemoragie, utilizând curba ROC (receiver-operating-characteristic). **Rezultate:** Comparând valoarea obținută la Fibroscan între loturile A și B avem următoarele ezultate: 41,07 ± 2,121 în grup A (pacienți cu hemoragie variceală) față de 27,77 ± 1,463 din grupa B (pacienții fără sângerare) (p <0,001 extrem de semnificativ). O valoare de 32 KPa poate prezice hemoragia variceală cu o sensibilitate de 58,44 și o specificitate de 72,22. AUROC = 0.695 (p = 0.0001), VP+ (valoare predictivă pozitivă) = 69,2, VP- (valoare predictivă negativă) = 61,9, interval de încredere 95% (0,614 - 0,768). O valoare de 62,5 KPa poate prezice hemoragia cu o valoare predictiv pozitivă de peste 90%. **Concluzie:** Elastografia hepatică este o metodă noninvazivă fiabilă pentru aprecierea riscului de hemoragie variceală la pacienții cu ciroză hepatică.

Cuvinte cheie: varice esofagiene, hemoragie variceală

ABSTRACT

Introduction: Fibroscan is a new noninvasive method able to evaluate the severity of fibrosis in patients with chronic liver diseases. **Aim:** Purpose of this study was to determine if fibroscan values correlate with variceal bleeding risk. **Material and method:** A retrospective study was performed on 149 patients with liver cirrhosis divided in 2 groups: batch A with variceal hemorrhage (72 cases) and batch B without bleeding (77cases). We compared the fibroscan values between the two groups using the unpaired t-test and we have established a cut-off fibroscan value for the risk of bleeding using ROC (receiver-operating-characteristic) curve. **Results:** Comparing the value of fibroscan between batch A and B we have the following results: 41.07± 2.121 in group A - patients with variceal hemorrhage, versus 27.77 ± 1.463 in group B - patients without bleeding ($p < 0.001$ extremely significant). Using ROC (receiver-operating-characteristic) curve we established a cut-off fibroscan value of 32 KPa for the risk of bleeding in our study with a sensitivity of 58.44 and specificity of 72.22. AUROC (areas-under-the-receiver-operating-characteristic curve) 0.695 (p=0.0001), +PV (positive predictive value)=69.2, -PV (negative predictive value)=61.9, 95% confidence Interval (0.614 to 0.768). **Conclusion:** The differences between the two groups are extremely significant in our study, therefore we can conclude that Fibroscan is a reliable noninvasive method for the detection of variceal bleeding risk.

Key Words: cut-off fibroscan value, esophageal varices, variceal bleeding

INTRODUCTION

Progressive hepatic fibrosis with the development of cirrhosis is a feature of almost all chronic liver diseases. Liver biopsy is currently considered the gold standard for assessing hepatic fibrosis. However, it is an invasive and painful procedure, with rare but potential life threatening complications, limiting its acceptance and repetition in usually asymptomatic patients.[1,2]

Clinic of Gastroenterology, Clinical Emergency Hospital, Timisoara

Correspondence to:
Iulia Ratiu, Clinic of Gastroenterology, Clinical Emergency Hospital, 10 Dr. I. Bulbuca Blvd., Timisoara
Email: ratiu_iulia@yahoo.com

Received for publication: Oct. 22, 2008. Revised: Jan. 14, 2009.

In addition, the accuracy of liver biopsy in assessing fibrosis may be questioned because of sampling error and interobserver variability, which may lead to understaging of cirrhosis.[3-6] Thus there is a need to develop and validate non-invasive tests that can accurately reflect the full spectrum of hepatic fibrosis, cirrhosis, and its severity in liver diseases.

Transient elastography (FibroScan) is a new and promising noninvasive and rapid method for the diagnosis and quantification of hepatic fibrosis in patients with chronic liver disease. It was originally developed to detect solid malignancies in soft tissues such as breast cancer and prostate cancer.[7] The system is equipped with a probe consisting of an ultrasonic transducer mounted on the axis of a vibrator. A vibration of mild amplitude and low frequency is transmitted from the vibrator to the tissue by the transducer itself. This vibration induces an elastic shear wave which propagates through the tissue. In the meantime, pulse-echo ultrasonic acquisitions are

performed to follow the propagation of the shear wave and measure its velocity, which is directly related to tissue stiffness (or elastic modulus). The harder the tissue, the faster the shear wave propagates. Acquisition time is less than 100 ms and can therefore be used in moving tissues. Sample size is increased by repeated measurements and by increasing measurement depth from 25 to 65 mm, the FibroScan® is more likely to "hit" an affected area since fibrosis may be focal. Results of liver elasticity are expressed in kilopascals (KPa). The scan can be performed easily; it is inexpensive and produces no side effects. Patients only feel the probe pressure in the intercostal space without anticipated pain. Obesity, ascites and narrow intercostal spaces are physiological boundaries that hamper the accuracy of the test. Sometimes, it may be virtually impossible to take measurements in such patients.[8]

Liver stiffness measurement using FibroScan is reproducible and independent of the operator.[9]

Some recent extensive studies, have demonstrated that measurement of liver stiffness with FibroScan® is a good alternative for liver biopsy. The amount of fibrosis can be quantified very easily and reliably and is feasible in more than 95% of the patients.[10-12] In cirrhotic patients, liver stiffness measurements range from 12.5 to 75.5 kPa. However, the clinical relevance of these values is unknown. FibroScan® values ranged from 2.4 to 75.4 kilopascals (median: 7.4 kilopascals). Cut-off values were 7.1 kPa for F ≥ 2, 9.5 kPa for F ≥3 and 12.5 kPa for F = 4 (defined according to the METAVIR classification system).[13-17]

The risk of variceal haemorrhage is clearly related to the size of esophageal varices Therefore primary prevention of variceal bleeding applies to patients with previously diagnosed large esophageal varices (grade II or III) detected by periodical upper tract endoscopy (Baveno IV and AASLD Consensus). A generalized program of periodical upper tract endoscopy in these patients might result in heavy economical burden even for developed countries. Furthermore repeated examinations, when not performed under profound sedation, are often poorly accepted by patients who may refuse further follow up.

FibroScan® can be used indirectly to predict the presence of portal hypertension. Liver stiffness measurement may allow predicting the presence of large esophageal varices in patients with cirrhosis and may help to select patients for endoscopic screening.[18-21]

AIM OF THE STUDY

The purpose of this study was to determine if FibroScan can be used indirectly to predict the presence of portal hypertension and the risk of variceal bleeding. In the present the Baveno IV and AASLD Consensus recommend to screen all cirrhotic patients for esophageal varices. If liver stiffness measurement allows predicting the presence of large esophageal varices in patients with cirrhosis we could select the patients for endoscopic screening.

MATERIAL AND METHOD

We studied 149 patients with liver cirrhosis and esophageal varices grade II and III. Patients with hepatocarcinoma were excluded. In accordance with history of variceal bleeding we divided this batch into 2 groups:

- Batch A with hemorrhage (72 cases);
- Batch B without bleeding episodes (77 cases).

In all patients we performed liver stiffness measurement with the Fibroscan® (Echosens device). Measurements were performed on the right lobe of the liver through intercostal spaces, on patients lying in the dorsal decubitus position with the right arm in maximal abduction. The tip of the probe transducer was covered with coupling gel and placed on the skin, between the rib bones at the level of the right lobe of the liver. The operator, assisted by an ultrasonic time-motion image, located a liver portion of at least 6 cm thick free of large vascular structures. Once the measurement area had been located, the operator pressed the probe button to start an acquisition. Measurement depth was between 25 mm and 65 mm below the skin surface. Measurements which did not have a correct vibration shape or a correct follow up of the vibration propagation were automatically rejected by the software. Up to 10 successful measurements were performed on each patient. Success rate was calculated as the ratio of the number of successful measurements over the total number of acquisitions. The results are expressed in kilopascal (kPa). Median value of the successful measurements was kept as representative of liver stiffness. Only liver stiffness measurements obtained with at least five successful measurements and a success rate of at least 30% were considered reliable.

We compared the fibroscan values between the two groups and we established a cut-off fibroscan value for the risk of bleeding using GraphPad Prism statistic program.

RESULTS

We divided our batch of patients into two groups:
- A - with hemorrhage (72 cases);

- B - without bleeding episodes (77cases).

Comparing the value of fibroscan between the two groups we have the following results:

- 41.07 ± 2.417 in group A – patients with variceal hemorrhage versus

- 27.77 +/- 1.724 in group B- patients without bleeding. (Fig. 1)

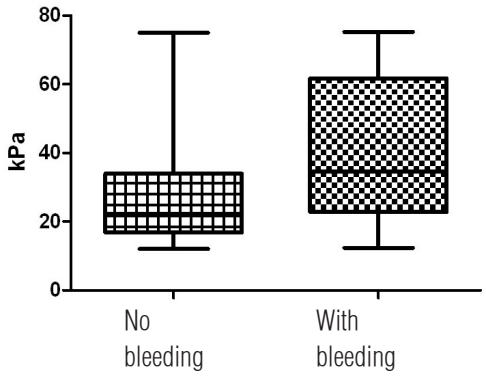

Figure 1. Comparison of Fibroscan values.

Using unpaired t-test we found a significant difference between the fibroscan values from the two groups: P < 0.0001 (ES); difference between means -13.29 ± 3.005, 95% confidence interval -19.18 to -7.403.

The F-test was used to evaluate the difference among the means: F=2.102, DFn (degrees of freedom of numerator) =7 6, Dfd (degrees of freedom of denominator) = 71, P = 0.0018

Using ROC curve we established the cut-off fibroscan value > 32 for the risk of bleeding in our study with a sensitivity of 58.44 and specificity of 72.22. AUROC (areas-under- the-receiver-operating-characteristic curve) = 0.695 (p=0.0001), +PV = 69.2, -PV = 61.9, CI 95% (0.614 to 0.768). (Fig. 2)

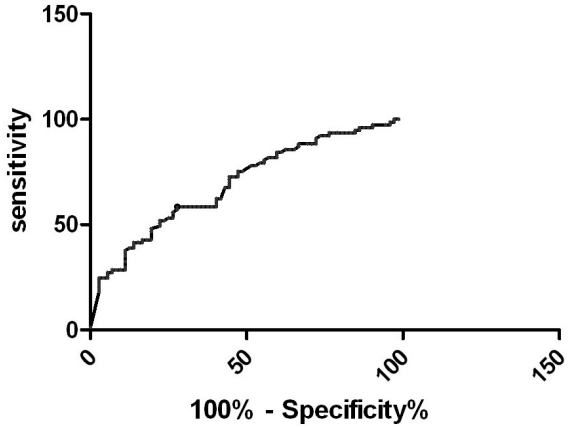

Figure 2. The ROC curve.

After establishing the cut-off value for the best sensitivity and specificity we identified a value of 62.8 kPa which can predict variceal bleeding with a positive predictive value above 90%.

DISCUSSION

In previous studies, a liver stiffness measurement value < 19 kPa was highly predictive of the absence of esophageal varices grade ≥ II, the cut off for the presence of esophageal varices stage 2/3 was ranged from 27.5 to 35 kPa, and for esophageal bleeding 62.7 kPa.[22-24].

In other studies TE (transient elastography) was not accurate in prediction of esophageal varices, with an AUROC ranging from 0.76 to 0.84.[25] Although the sensitivity was good (71%-96%), specificity and positive predictive values (PPV) were low (60%-80% and 48%-54%) and overall accuracy was inferior compared to simple tests, like platelet count/spleen diameter ratio.[26]

Another problem arising from these studies is the wide range of proposed cut-offs, varying from 13.9 to 21.3 KPa for all varices, from 19 to 30 KPa for grade 2 varices and from 55 to 63Kpa for bleeding varices. The optimal cut offs therefore are still to be defined.[27-28] Foucher et al assessed the accuracy of FibroScan for the detection of large oesophageal varices and the risk of variceal bleeding in patients with chronic liver disease. For the presence of esophageal varices stage 2/3, and esophageal bleeding were 27.5, and 62.7 kPa, respectively. The authors concluded that Fibroscan use for the follow-up and management of these patients could be of great interest and should be evaluated further.[28]

Rudler et al reported their data on consecutive patients admitted to the intensive care unit with variceal hemorrhage who underwent hepatic venous pressure gradient (HVPG) measurement and transient elastography.[29] With an HVPG cutoff > 20 mm Hg (HVPG > 20 mm Hg is an independent predictor of death in patients with cirrhosis and variceal bleeding), 8 patients were enrolled, but 4 could not undergo elastography, because of severe ascites. Correlation between liver stiffness and HVPG was poor. The study authors concluded that transient elastography is unlikely to be of utility in this patient population.

Klibansky had more success in describing a useful application of transient elastography to predict clinical outcomes in cirrhosis.[30] Clinical endpoints were defined as the development of ascites or encephalopathy, variceal bleeding, development of hepatocellular carcinoma, or liver transplantation. Multivariate analysis indicated that the only independent predictors of outcome were Child-Pugh score and liver stiffness.

The 2008 annual AASLD meeting provided exciting insights into the future of hepatology.[31] In the field of cirrhosis and its complications, several important advances stand out. Tthe development of noninvasive techniques to provide diagnostic and prognostic information in patients with cirrhosis is making progress.

Finally, Castera has concluded that Fibroscan could be a valuable tool for the detection of esophageal varices and discriminates the patients with large esophageal varices with the risk of bleeding. However, optimal cut-offs vary from study to study, therefore, optimal transient elastography cut-off remains to be defined.[32]

Due to the controversial results of all the studies described above we wanted to evaluate the value of transient elastography in prediction of variceal hemorrhage in our patients.

The results of our study showed that transient elastography is an useful technique for evaluating the risk of variceal bleeding in cirrhotic patients. With a cut off value of 32 kPa, negative and positive predictive values for the bleeding risk were 61.9% and 69.2%, respectively.

For the > 32 criterion, cut-off value were chosen to maximize the sum of sensitivity and specificity whereas for the > 62.8 criterion we have chosen a cut-off value to have a positive predictive value of more than 90%, which favors specificity. In clinical practice, such results could be of major relevance for follow-up of patients with cirrhosis. (Table 1)

Table 1. Fibroscan cut off values.

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	-LR	+PV	-PV
> 32 *	58.44	46.6–69.6	72.22	60.4–82.1	2.10	0.58	69.2	61.9
>62.8	24.68	15.6–35.8	97.22	90.3–99.6	8.88	0.77	90.5	54.7

+LR: Positive likelihood ratio
-LR: Negative likelihood ratio
+PV: Positive predictive value
-PV: Negative predictive value

Cirrhosis places the patient at risk of clinical complications, such as portal hypertension, and variceal rupture is the second cause of death in cirrhosis, justifying early screening for esophageal varices. The usual means of diagnosing esophageal varices is upper gastrointestinal endoscopy. However, endoscopy can be considered invasive due to the technique and level of discomfort and the last recent consensus not recommend endoscopic screening for evaluating the risk of bleeding in patients with esophageal varices grade 2 or 3. Non-invasive methods for diagnosis need to be developed. In our study we establish a fibroscan 32 KPa cutt of value for the risk of bleeding and we recommend endoscopic evaluation for those patients. A cut-off value above 62.8 correlates with a positive predictive value above 90% which means those patients have a very high risk of bleeding despite their primary prophylactic treatment with propranolol. Thus, a prospective study in clinical practice should be done; we recommend the prophylactic ligation in patients with liver stiffness values of more than 62.8 kPa.

CONCLUSION

In conclusion, liver stiffness measurement may be accurate for assessing the risk of variceal hemorrhage in cirrhotic patients. However, a longitudinal cohort study needs to be performed to predict the complications of cirrhosis using FibroScan so that endoscopic evaluation of varices grade 2 and 3 and prophylactic variceal ligation in selected cases should be performed.

REFERENCES

1. Cadranel JF, Rufat P, Degos F. Practices of liver biopsy in France: results of a prospective nationwide survey. For the Group of Epidemiology of the French Association for the Study of the Liver (AFEF). Hepatology 2000;32:477–81.
2. Bravo AA, Sheth SG, Chopra S. Liver biopsy. N Engl J Med 2001;344:495–500.
3. Maharaj B, Maharaj RJ, Leary WP, et al. Sampling variability and its influence on the diagnostic yield of percutaneous needle biopsy of the liver. Lancet 1986;1:523–5.
4. Regev A, Berho M, Jeffers LJ, et al. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. Am J Gastroenterol 2002;97:2614–18.
5. Bedossa P, Dargère D, Paradis V. Sampling variability of liver fibrosis in chronic hepatitis C. Hepatology 2003;38:1449–57.
6. Colloredo G, Guido M, Sonzogni A, et al. Impact of liver biopsy size on histological evaluation of chronic viral hepatitis: the smaller the sample, the milder the disease. J Hepatol 2003;39:239–44
7. Sandrin L, Tanter M, Gennisson JL, et al. Shear elasticity probe for soft tissues with 1D transient elastography. Ultrason Ferroelectr Freq Control 2002;49:436–46.
8. Verveer C, de Knegt RJ. Non-invasive measurement of liver fibrosis: Application of the FibroScan® in hepatology. Scand J Gastroenterol Suppl 2006;243:85-8.
9. Sandrin L, Fourquet B, Hasquenoph JM, et al. Transient elastography: a new non-invasive method for assessment of hepatic fibrosis. Ultrasound Med Biol 2003;29:1705–13.
10. Castra L, Vergniol J, Foucher J, et al . Prospective comparison of transient elastography, Fibrotest, APRI and liver biopsy for the assessment of fibrosis in chronic hepatitis C. Gastroenterology 2005;128:343-50.
11. Friedrich-Rust M, Ong MF, Herrmann E, et al . Real-time elastography for noninvasive assessment of liver fibrosis in chronic viral hepatitis. AJR Am J Roentgenol 2007;188:758-64.
12. Foucher J, Castra L, Bernard PH, et al. Prevalence and factors associated with failure of liver stiffness measurement using FibroScan® in a prospective study of 2114 examinations. Eur J Gastroenterol Hepatol 2006;18:411-2.

13. Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. Hepatology 1996;24:289-93.
14. Foucher J, Chanteloup E, Vergniol J, et al . Diagnosis of cirrhosis by transient elastography (FibroScan®): A prospective study. Gut 2006;55:403-8
15. Nguyen-Khac E, Capron D. Noninvasive diagnosis of liver fibrosis by ultrasonic transient elastography (Fibroscan). Eur J Gastroenterol Hepatol 2006;18:1321-5.
16. Nguyen-Khac E. Results and place of Fibroscan in the non-invasive diagnosis of hepatic fibrosis. Rev Med Interne 2007;28:94-102.
17. Ganne-Carrit N, Ziol M, de Ledinghen V, et al . Accuracy of liver stiffness measurement for the diagnosis of cirrhosis in patients with chronic liver diseases. Hepatology 2006;44:1511-7.
18. Del Poggio P, Colombo S. Is transient elastography a useful tool for screening liver disease? World J Gastroenterol 2008;15(12):1409-14.
19. Pritchett S, Afdhal N. The optimal cutoff for predicting large esophageal varices using transient elastography is disease specific, DDW 2008 Abstracts.
20. Vizzutti F, Arena U, Romanelli R, et al. Liver stiffness measurement predicts severe portal hypertension in patients with HCV-related cirrhosis. Hepatology 2007;18:133-8.
21. Lim JK, Groszmann RJ. Transient elastography for diagnosis of portal hypertension in liver cirrhosis: Is there still a role for hepatic venous pressure gradient measurement? Hepatology 2007;45(5):1087-90.
22. Kazemi F, Kettaneh A, N'kontchou G, et al. Liver stiffness measurement selects patients with cirrhosis at risk of bearing large oesophageal varices. J Hepatol 2006;45:230-5.
23. Foucher, E Chanteloup, J Vergniol,Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study. Gut 2006;55(3):403-8.
24. Khokhar A, Farnan R, MacfarlaneC. Liver stiffness and biomarkers: Correlation with extent of fibrosis, portal hypertension and hepatic synthetic function. 56th Annual Meeting of the American Association for the Study of Liver Disease, Nov. 11-15, 2005, San Francisco, USA.
25. Lim JK, Groszmann RJ. Transient elastography for diagnosis of portal hypertension in liver cirrhosis: is there still a role for hepatic venous pressure gradient measurement? Hepatology 2007;45:1087-90.
26. Giannini E, Botta F, Borro P, et al. Platelet count/spleen diameter ratio: proposal and validation of a non-invasive parameter to predict the presence of oesophageal varices in patients with liver cirrhosis. Gut 2003;52:1200-5.
27. Castera L, Bernard PH, Le Bail B, et al. What is the best non invasive method for early prediction of cirrhosis inchronic hepatitis C? Prospective comparison between Fibroscan and serum markers. Hepatology 2007;46:A581.
28. Foucher J, Chanteloup E, Vergniol J, et al. Diagnosis of cirrhosis by transient elastography (FibroScan): A prospective study. Gut 2006;55(3):403-8.
29.Rudler MCluzel P, Massard J, et al. Transient elastography (Fibroscan) and hepatic venous pressure gradient measurement in patients with cirrhosis and gastrointestinal haemorrhage related to portal hypertension. Hepatology 2008;48:324A.
30. Klibansky D, Blanco PG, Kelly E, et al. Liver stiffness predicts clinical outcomes in patients with chronic liver disease. Hepatology 2008;48:1057A.
31. Herrine SK. Issues in cirrhosis and portal hypertension The Liver Meeting 2008: 59th Annual Meeting of the American Association for the Study of Liver Diseases.
32. Castera L, Le Bail B, Roudot-Thorava 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