Original Article

The Prediction Values of Transient Elastography for Clinically Significant Esophageal Varices in Patients with Liver Cirrhosis

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ABSTRACT

Background: Endoscopic variceal surveillance is recommended in patients with liver cirrhosis. However, the procedure is invasive and needs an experienced endoscopist. Recent study showed that liver stiffness measurement (LSM) was correlated with cirrhosis and portal hypertension. The aim of this study was to evaluate the role of transient elastography in predicting presence of esophageal varices that require primary the prophylaxis.

Methods: Cirrhotic patients without history of upper gastrointestinal bleeding underwent LSM with transient elastography followed by upper gastrointestinal endoscopy. Clinically significant esophageal varices were defined as esophageal varices ≥ grade II and/or presence of red wale sign. Relationship between LSM and clinically significant esophageal varices was analyzed in all patients.

Results: A total of 52 patients, 35 male and 17 female, were enrolled in this study. Forty-seven patients had CTS class A. The median age was 58. Clinically significant esophageal varices were noted in 14 patients. The means LSM were 30.2 and 15.5 kPa in patients with and without clinically significant esophageal varices respectively. Patients with clinically significant esophageal varices had significantly higher liver stiffness scores than those without ($p < 0.001$). ROC curve analysis showed that LSM value less than 16.2 kPa was a predictor of clinically significant esophageal varices (sensitivity: 85%, PPV: 41%, NPV: 91% and area under the curve was 0.81).

Conclusion: LSM less than 16.2 kPa was a predictor of the absence of clinically significant esophageal varices with 91% NPV. The result may be useful in identifying patients who do not require endoscopic procedure.

Key words : Transient elastography, esophageal varices, liver cirrhosis

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INTRODUCTION

Liver cirrhosis represents a late stage of progressive hepatic fibrosis characterized by distortion of hepatic architecture and formation of regenerative nodules. The prevalence of cirrhosis is high in Asian and African countries where chronic viral hepatitis B or C are common[1]. Clinically significant portal hypertension is considered when the level of portal pressure is at risk for developing complications. Portal hypertension is a contributing factor for the development of ascites and hepatic encephalopathy. Furthermore, it is a direct cause of variceal haemorrhage which can be fatal[2] Patients with cirrhosis and gastroesophageal varices have HVPG of at least 10 mmHg[3-4]. Esophageal varices are detected in about 30-60% of patients with liver cirrhosis, depending on the severity of portal hypertension. New varices appear at the rate of 5-10%, and progression from small to large varices is between 5 and 30%[5-6]. Current guidelines recommend screening all cirrhotic patients with an upper GI endoscopy at the time of diagnosis of cirrhosis. Patients with compensated cirrhosis without varices at screening endoscopy should undergo surveillance endoscopy every 3-year. Patients with small varices at screening endoscopy should undergo surveillance endoscopy every 1-2 year, and 1-year interval should be implemented in decompensated patients with or without varices. All patients with medium to large varices should be endoscopic treated to prevent variceal haemorrhage[2], whilst patients without varices or with small varices without red wale sign do not necessarily need primary prophylaxis. In any case, upper GI endoscopy is an invasive procedure requiring an experienced endoscopist and is associated with potential complications including aspiration, bleeding and over-sedation, and routine periodic endoscopic screening in all cirrhotic patients, especially low-risk patients, increase medical workload and unwanted complication.

Liver stiffness measurement (LSM), or transient elastography, is calculated from the velocity of low-frequency elastic wave inside the liver. Transient elastography is a non-invasive assessment of liver fibrosis based on elastometry. Advantages of this method include painlessness, rapidity (taking less than 5 minutes) and ease of perform and both at bedside and in the outpatient clinic. The volume of liver substance measured is more than 100 times over biopsy sample, representing larger area of examined hepatic parenchyma. Normal range of liver stiffness is between 2.5 and 75 kPa[7]. A recent study showed that transient elastography was an excellent diagnostic tool to diagnose cirrhosis regardless of the underlying etiology[8]. LSM is used as a non-invasive tool to identify chronic liver disease patients with severe portal hypertension who would benefit from further standard investigations such as upper GI endoscopy and hemodynamic studies[9]. Kazemi et al. demonstrated the utility of LSM as a predictor of esophageal varices and showed that a cut off value of less than 19 kPa was highly predictive of the absence of oesophageal varices smaller than grade II[10]. The aim of the present study was to evaluate correlation between transient elastrographic findings and presence of esophageal varices.

Patients and methods

This study was a prospective study. Sixty adult patients aged 18 or over were included. The diagnosis of liver cirrhosis was based on imaging study, operative findings or pathological confirmation. All tests were performed at Songklanagarind hospital, Hat Yai, Thailand, between January 2009 and December 2009. Exclusion criteria were (1) presence of moderate to tense ascites, (2) body mass index (BMI) ≥ 30, (3) history of variceal bleeding, (4) history of hepatic resection or shunt surgery, (5) alcoholic hepatitis, (6) acute viral hepatitis or hepatitis flare, and (7) hepatocelluar carcinoma. Written informed consents were obtained from all participants.

LSM was assessed on the liver right lobe by transient elastography prior to performing upper GI endoscopy for variceal screening. The probe was placed on the first right intercostal space, at the intersection between the mid-axillary line and the level of xiphoid process. If this point was not technically possible, measurement was made where adequate images by M and A modes could be obtained. At least 10 successful measurements were taken for each patient. An interquartile range lower than 30% of the median value and a minimum success rate of 80% were required for a valid result[11-12]. Liver stiffness was expressed in kiloPascal (kPa). Upper gastrointestinal endoscopy was performed within 24 hours by one of two experienced endoscopists or three well-trained GI fellows who were not aware of the LSM report. Clinically significant esophageal varices were defined as varices bigger than than 5 mm and/or with presence of red wale signs. Age, sex, etiology of cirrhosis, albumin level, platelet count,

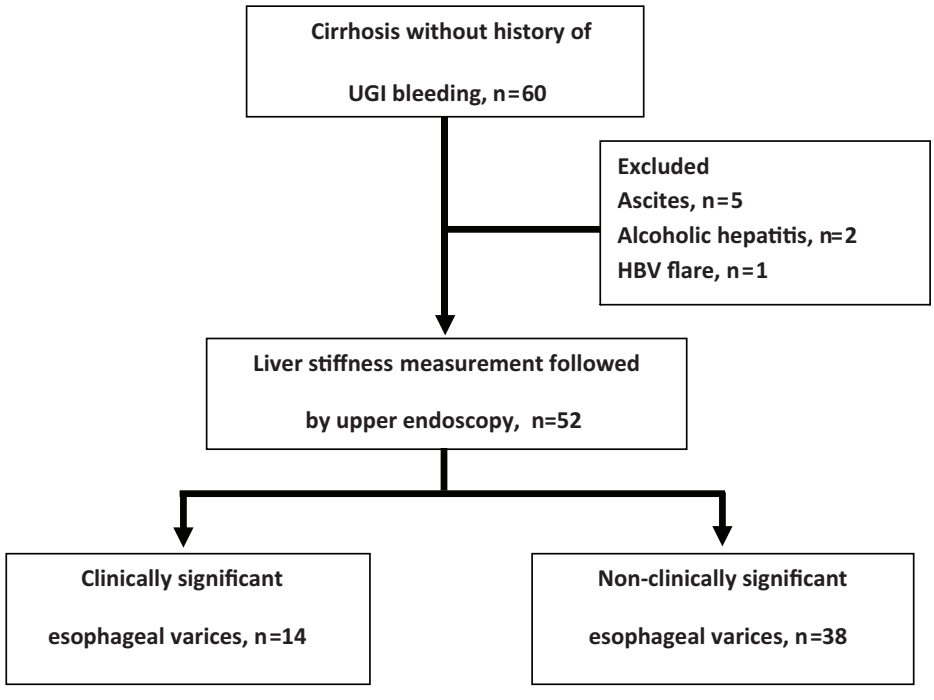

Figure 1. Flow diagram of study patients.

prothrombin activity, serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT) and Child-Pugh score were also recorded.

Statistical analysis

Demographic data of patients with or without clinically significant esophageal varices were compared, using student's t test for continuous variables and exact Fisher's test for categorical variables. The receiver-operating characteristics (ROC) curve was calculated. The areas under the curve as well as 95% confidence interval were calculated with R software. Efficiency of LSM for the prediction of presence of clinically significant esophageal varices was evaluated in this study. The relationship between LSM values and presence of clinically significant esophageal varices was evaluated. Statistical analysis was performed with the R software version 2.5.1[13].

Results

Sixty cirrhotic patients without history of upper gastrointestinal bleeding were enrolled. Five patients with moderate to tense ascites, two alcoholic hepatitis patients with elevated ALT, and one hepatitis-B patient with ALT flare were excluded. Of the remaining 52 patients, 67% were men. All underwent liver stiffness measurement and upper gastrointestinal endoscopy. The mean age was 55. The most common cause of cirrhosis was hepatitis B (42.3%). Other causes were alcohol (23.1%), hepatitis C (13.5%), nonalcoholic steatohepatitis (13.5%) and miscellaneous (5.8 %). The mean platelet count was $135 \pm 82*10^3/mm^3$. Fourty-seven patients were Child - Pugh class A (90.4%), 4 were class B (7.7%), and 1 was class C (1.9%). Clinically significant esophageal varices were noted in 14 patients. Of these, 13 had EV grade II-III, and only 1 had EV grade I with red wale sign. There were no significant differences of baseline clinical characteristics between the group with and without clinically significant esophageal varices. Baseline clinical characteristics are shown in Table 1.

LSM and clinically significant esophageal varices

The median LSM value was significantly higher in those with clinically significant esophageal varices than in those without (30.2 ± 13.2 vs. 15.5 ± 9.6 kPa, $p< 0.001$) (Figure 2). The ROC curve was analyzed to identify the best cut-off value of LSM that would easy and practical to use as a predictor of clinically significant esophageal varices. The positive predictive value and the negative predictive value for the different cut off values are shown in Table 2. LSM 16.2 kPa was

Table 1. Baseline demographic characteristics of the study groups.

	All patients (n=52)	Non-clinically significant esophageal varices (n=38)	Clinically significant esophageal varices (n=14)	*p*-value
Age (yrs.)	55.7 ± 12.3	56.3 ± 11.4	54 ± 14.8	0.59
Male (%)	67%	68.4%	64.3%	1.0
Etiology of cirrhosis (n,%)				
Alcohol	12 (23.1)	8 (21.1)	4 (28.6)	
HBV	22 (42.3)	19 (50.0)	3 (21.4)	
HCV	7 (13.5)	3 (7.9)	4 (28.6)	0.19
NAFLD	7 (13.5)	5 (13.2)	2 (14.3)	
Miscellaneous	3 (5.8)	3 (7.9)	1 (7.1)	
Platelets (10^3/mm^3)	135 ± 82	144 ± 92	111 ± 40	0.51
Albumin (g/dL)	3.99 ± 0.66	4.21 ± 0.58	3.6 ± 0.74	0.22
Serum AST (U/L)	54 ± 43	45 ± 20	79 ± 72	0.15
Serum ALT (U/L)	42 ± 25	37 ± 20	53 ± 32	0.22
PT (INR)	1.09 ± 0.17	1.04 ± 0.12	1.22 ± 0.23	0.15
Child-Pugh score A/B/C	90.4/7.7/1.9	5.3 ± 0.81	6.0 ± 1.77	0.18

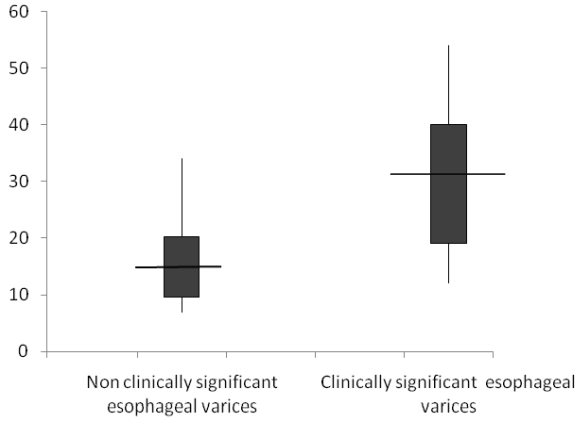

Figure 2. Comparison of LSM values for non-clinically significant esophageal varices and clinically significant esophageal varices.

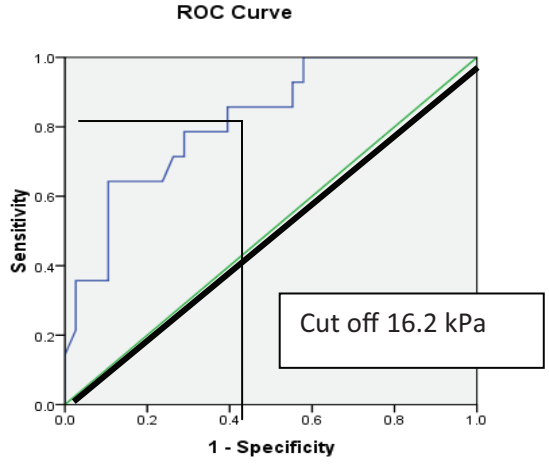

Figure 3. Receiver-operating characteristics curve of liver stiffness measurement for predicting clinically significant esophageal varices. AUROC = 0.83; 95% CI (0.69-0.9).

Table 2. Diagnostic indices for predicting clinically significant esophageal varices for different LSM values.

LSM value	Sensitivity	Specificity	+LR	-LR	PPV	NPV
13.0 kPa	92%	50%	1.84	0.16	40%	95%
16.2 kPa*	85%	55%	1.88	0.27	41%	91%
19.5 kPa	78%	60%	1.95	0.36	42%	88%

*Best LSM cut-off value chosen

chosen as the best cut-off value as it provided 41% positive predictive value and 91% negative predictive value, with area under the curve (AUC) of 0.83, 95% CI (0.69-0.9). With this cut-off value, 46% form our study population would not need gastroscopy.

Discussion

Several non-endoscopic screening tools and tests have recently been reported to identify esophageal varices in cirrhotic patients that require primary prophylactic treatments. The main purpose of such tools was to help avoid unnecessary and unpleasant endoscopy with its associated complications and heavy workload in the endoscopy with Kazami and colleague demonstrated that LSM helped predict the presence of large oesophageal varices in patients with cirrhosis and select patients for endoscopic screening[10]. Our prospective randomized single-blinded controlled study showed that LSM, a simple non-invasive physical parameter, could identify patients with clinically significant esophageal varices, the mean value being significantly higher than in those without clinically significant esophageal varices (30.2 ± 13.2 vs. 15.5 ± 9.6 kPa, $p<0.001$). An optimal cutoff LSM value >16.2 kPa was highly predictive of the presence of clinically significant esophageal varices with sensitivity, specificity, positive predictive value and negative predictive value of 85%, 55%, 41% and 91% respectively. The cut-off LSM value in our study was lower than that reported by Kazami (16.2 vs. 19 kPa). This difference was probably due to smaller average body size for Thai patients compared with Caucasians. The most common cause of liver cirrhosis in our study was hepatitis B, whereas HCV was the case in the previous study. Different etiologies of cirrhosis were also contributing. The use of LSM has limitations, however, as the technique is not useful in patients with ascites and in over weight subjects.

Conclusion

Measurement of liver stiffness helps predict the presence of clinically significant esophageal varices in patients with liver cirrhosis. LSM value less than 16.2 kPa strongly predicts absence of clinically significant esophageal varices with 91% negative predictive value. LSM may thus be a potential tool for selecting cirrhotic patients who do not require upper endoscopy procedure surveillance.

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