Original Article

Spleen Stiffness as Predictor of Esophageal Varices and Portal Hypertensive Gastropathy in Cirrhotic Patients

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ABSTRACT

Background: Esophageal varices (EV) and portal hypertensive gastropathy (PHG) are consequences of portal hypertension (PH) and potentially predispose to bleeding complications in cirrhotic patients. To detect these lesions, especially EV, an esophago-gastro-duodenoscopy (EGD) is mandatory and is recommended as standard of care in clinical guidelines. An alternative non-invasive test is ideally preferred in order to reduce the endoscopy unit workload as well as to improve patients' compliance. The density of the spleen is altered in the portal hypertensive state which induces tissue hyperplasia and fibrosis. Thus, measured and quantified by transient elastography may be used to predict the presence and the grading of EV, as well as the occurrence of PHG.

Objective: We aimed to investigate the utility of spleen stiffness for the evaluation of EV and PHG in cirrhotic patients attending Bhumibol Adulyadej Hospital, Bangkok.

Methods: Spleen stiffness (SS) in 59 cirrhotic patients was evaluated by using FibroScan®. All patients were underwent EGD for diagnosis and grading severity of EV and PHG.

Results: Forty-six of 59 patients (78%) had a valid SS measurement. Twenty-eight patients (60.9%) had EV (F1; n = 13, F2; n = 12, F3; n= 3) and 33 (71.7%) had PHG (mild; n = 26, moderate to severe; n = 7). SS was both significantly higher in patients with EV compared to those without EV, and also in patients with PHG compared to those without. There was no significant difference of SS between the small (F1) and the large EV (F2 and F3) groups, nor between the mild and the moderate to severe PHG groups.

Conclusion: SS may be useful as a non-invasive tool for predicting the presence but not the grading of EV and PHG in cirrhotic patients.

Key words : Speen stiffness, Esophageal varices, Portal hypertensive gastropathy

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Introduction

Esophageal varices (EVs) is a major complication of liver cirrhosis and portal hypertension (PHT). The prevalence of EV has been reported to be 50% in cirrhotic patients[1], and mortality following an episode of variceal bleeding episode ranges 10-20%. Esophagogastro-duodenoscopy (EGD) for EV screening and grading is recommended as the standard of care according to current guidelines for providing proper surveillance and interventions[2].

In addition, portal hypertensive gastropathy (PHG), which is consequent of PHT, is another potential cause of bleeding in patients with liver cirrhosis[3]. PHT is essential in the development of PHG, and portal pressure is higher in patients with severe lesions. Bleeding seems to be more frequently associated with greater severity of the lesions[4].

Although there are no current guidelines, detecting PHG may help identify cirrhotic patients at risk of bleeding.

Efforts have been made to search for an ideal noninvasive method for evaluating the presence and the grading of EV in order to decrease the burden of the endoscopic unit, reduce medical personnel and the cost of care, and also to improve patient's compliance.

Several studies have shown that measurement of liver stiffness (LS) by transient elastography (TE) using FibroScan® may represent a rapid and non-invasive method for predicting the presence of clinically significant or severe PHT. However, LS correlates poorly with at higher HVPG and cannot differentiate the different grades of EV[5-9].

Splenomegaly is a common finding in liver cirrhosis because of vascular congestion, resistance to splenic vein outflow, tissue hyperplasia and fibrosis[10]. Changes of splenic density may be measured and quantified by TE as the spleen stiffness (SS) using FibroScan®[11,12]. FibroScan® has recently been used in literatures for the assessment of SS in cirrhotic patients[13,14]. Recent study showed that SS and LS were more accurate than other noninvasive parameters in detecting the presence EV in patients with hepatitis C virus-induced cirrhosis[12]. Similar conclusion was that SS in liver cirrhosis patients could predict the presence but not the grade of EV[11]. In Thailand, however, there were limited data describing the performance of SS using FibroScan® in cirrhotic patients. The aim of this study was to evaluate the utility of SS in predicting the presence and grading of EV in patients with liver cirrhosis attending Bhumibol Adulyadej Hospital. We also investigated whether SS is a useful tool for assessing of the presence and the grading of PHG.

Methods

Patients and study design

The study was carried out in cirrhotic patients attending the Gastrointestinal Unit, Bhumibol Adulyadej Hospital, Bangkok, between February 2014 and December 2014. The diagnosis of cirrhosis was based on clinical, biochemical and imaging (US and CT) data, plus liver biopsy in needed cases. Patients were excluded if they had tense ascites, history of active alcohol ingestion, active acute on chronic liver failure, hepatocellular carcinoma or other space-occupying lesions in the liver, biliary obstruction, and cardiac failure. Patients unwilling to participate in the study were also excluded.

A total of 59 patients were enrolled. All underwent TE of the liver and spleen for assessment of LS and SS. All patients were evaluated by EGD for EV and PHG documentation. Endoscopy was perform by experience GI fellows or staff. In case of uncertainty regarding the grading of EV and PHG, a second opinion was sought from another fellow or staff for a conclusion. Routine biochemical and hematologic parameters were recorded in every case.

Upper endoscopy

All patients underwent upper GI endoscopy. EVs were graded according to size; F1: small, straight; F2: enlarged, tortuous, occupying less than one-third of the lumen; and F3: large, coil-shaped, occupying more than one-third of the lumen. F1 was considered small whereas F2 and F3 were considered large. PHG were graded from endoscopic appearance; mild: mosaic-like pattern with pink central areola; and moderate to severe: a flat red spot in the center or diffusely red areola.

SS and LS measurement

SS and LS measurements were performed using TE (FibroScan®). The medium probe was used for all patients. Ten successful measurements were carried out on each patient. The median value was kept as a repre-

sentative of the liver and spleen stiffness, expressed in kilopascals (kPa). The results were considered unreliable if valid shots fewer than 10, success rate < 60%, or interquartile range >30 %[8]. The measurement failure was recorded when no value was obtained after at least 10 shots.

LS measurements were performed by standard procedure. For assessing SS, the patient's position was changed to supine with the left arm in maximum abduction and the transducer placed in the left intercostal spaces, usually on the posterior axillary line or directly over the palpable spleen below the costal space. The same quality thresholds as for LS measurement were used.

Statistical analysis

Continuous variables were presented as mean _ SD. Data were compared using t-test and Fisher's exact test. The diagnostic performance of SS was assessed using sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), accuracy, likelihood ratios (LR) and receiver operating characteristic (ROC) curves. The ROC curve is a plot of sensitivity versus 1-specificity for all possible cut-off values. The most commonly used index of accuracy is the area under the ROC curve (AUROC), with values close to 1 indicating higher diagnostic accuracy. Optimal cutoffs were chosen so that the sum of sensitivity and specificity would be maximal; positive and negative predictive values were computed for all calculated values.

RESULTS

Fifty-nine patients were enrolled in this study. Thirteen patients (22%) had no valid measurements and/ or unreliable results that did not meet the aforementioned valid measurement criteria, and were excluded from the study. SS measurements were unsuccessful in all 13 patients, and invalid measurable LS was the case in 7 patients. There were no differences in baseline biochemical, hematologic parameters and BMI between the patients with measurement failure and those with successful measurement (Table 1).

Overall, 46 patients were included. The etiology of cirrhosis was alcohol (n = 23, 50%), hepatitis B (n = 8, 17.4%), hepatitis C (n = 10, 21.7%), NASH (n = 4, 8.7%) and AIH (n = 1, 2.2%). Twenty-eight (61%) pa-

Table 1. Baseline characteristics of patients.

	Exclusion (n=13)	Inclusion (n=46)	*p*-value
Age	50 ± 9	52 ± 10	0.437
Gender			
- Male	12 (92.3%)	39 (84.8%)	
- Female	1 (7.7%)	7 (15.2%)	
BMI	22 ± 1	23 ± 2	0.207
Alb (mg/dL)	3.6 ± 0.4	3.4 ± 0.6	0.232
Plt (10^9/L)	163 ± 58	140 ± 60	0.219
AST (IU/L)	47 ± 22	57 ± 31	0.310
ALT (IU/L)	35 ± 10	38 ± 15	0.608
TB (mg/dL)	0.8 ± 0.4	1.2 ± 0.8	0.083
INR	1.13 ± 0.11	1.21 ± 0.13	0.060
EV			
- No EV	7 (53.8%)	18 (39.1%)	
- EV F1	6 (46.2%)	13 (28.3%)	
- EV F2	0 (0%)	12 (26.1%)	
- EV F3	0 (0%)	3 (6.5%)	
PHG			
- No PHG	5 (38.5%)	13 (28.3%)	
- Mild	8 (61.5%)	26 (56.5%)	
- Moderate/severe	0 (0%)	7 (15.2%)	

tients had EV (small, n = 13; large, n = 15). Thirty-three patients (72%) had PHG (mild, n= 26; moderate to severe, n=7) (Table 1). There were significant differences in platelets, INR and albumin in patients with EV compared with those without EV (Table 2). Conversely, there were no significant differences in any of these parameters in patients with and without PHG (Table 3).

Assessment of EV and PHG in liver cirrhosis patients by SS and LS

There were a significant differences in the mean LS (42.26 vs. 26.33 kPa, $p = 0.004$) and the mean SS (55.73 vs. 32.81 kPa, $p < 0.001$) between patients with EV versus those without EV (Table 2 and Figure 1). Although the mean SS was different significantly

Table 2. Characteristics of patients with and without EV.

Variables	Total (n=46)	No EV (n=18)	EV (n=28)	*p*-value
Age	52.07 ± 10.21	52.78 ± 11.09	51.61 ± 9.79	0.709
Sex				
Male	39 (84.8%)	15 (83.3%)	24 (85.7%)	1.000
Female	7 (15.2%)	3 (16.7%)	4 (14.3%)	1.000
BMI	22.65 ± 1.99	23.34 ± 2.03	22.2 ± 1.87	0.056
Cause				
Alcohol	23 (50.0%)	7 (38.9%)	16 (57.1%)	
CHB	8 (17.4%)	6 (33.3%)	2 (7.1%)	
CHC	10 (21.7%)	3 (16.7%)	7 (25%)	
NASH	4 (8.7%)	1 (5.6%)	3 (10.7%)	
AIH	1 (2.2%)	1 (5.6%)	0 (0%)	
CTP				
A	23 (50.0%)	13 (72.2%)	10 (35.7%)	
B	23 (50.0%)	5 (27.8%)	18 (64.3%)	
Alb (mg/dL)	3.43 ± 0.61	3.72 ± 0.63	3.24 ± 0.53	0.007*
Plt (10^9/L)	139.98 ± 59.94	188.06 ± 65.71	109.07 ± 27.15	<0.001*
AST (IU/L)	56.78 ± 30.51	47.06 ± 27.41	63.04 ± 31.22	0.083
ALT (IU/L)	37.63 ± 15.33	33.56 ± 14.13	40.25 ± 15.74	0.150
TB (mg/dL)	1.25 ± 0.84	1.07 ± 0.93	1.36 ± 0.77	0.255
INR	1.21 ± 0.13	1.14 ± 0.1	1.25 ± 0.13	0.004*
LS (kPa)	36.03 ± 19.78	26.33 ± 15.75	42.26 ± 19.82	0.004*
SS (kPa)	46.76 ± 16.5	32.81 ± 13.03	55.73 ± 11.56	<0.001*

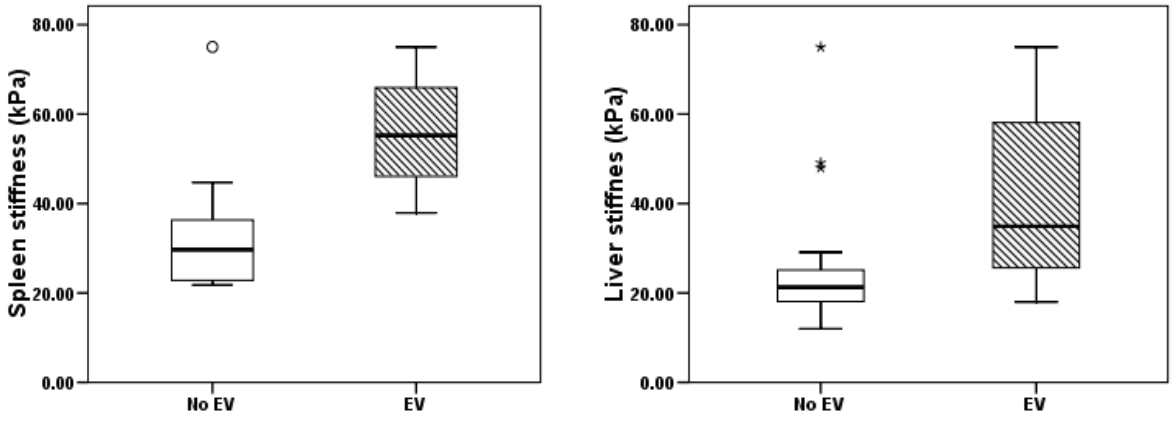

Figure 1. SS and LS in patients with and without EV.

Table 3. Characteristics of patients with and without PHG.

	Total (n=46)	No PHG (n=13)	PHG (n=33)	*p*-value
Age	52.07 ± 10.21	54 ± 9.26	51.3 ± 10.6	0.426
Gender				
- Male	39 (84.8%)	10 (76.9%)	29 (87.9%)	
- Female	7 (15.2%)	3 (23.1%)	4 (12.1%)	
BMI	22.65 ± 1.99	23.54 ± 1.25	22.3 ± 2.13	0.056
Cause				
- Alcohol	23 (50.0%)	3 (23.1%)	20 (60.6%)	
- CHB	8 (17.4%)	6 (46.2%)	2 (6.1%)	
- CHC	10 (21.7%)	2 (15.4%)	8 (24.2%)	
- NASH	4 (8.7%)	1 (7.7%)	3 (9.1%)	
- AIH	1 (2.2%)	1 (7.7%)	0 (.0%)	
CTP				
- A	23 (50.0%)	10 (76.9%)	13 (39.4%)	
- B	23 (50.0%)	3 (23.1%)	20 (60.6%)	
Alb (mg/dL)	3.43 ± 0.61	3.69 ± 0.81	3.32 ± 0.49	0.142
Plt (10^9/L)	139.98 ± 59.94	175.92 ± 82.68	125.82 ± 41.92	0.055
AST (IU/L)	56.78 ± 30.51	55.77 ± 28.36	57.18 ± 31.73	0.889
ALT (IU/L)	37.63 ± 15.33	39.85 ± 12.88	36.76 ± 16.29	0.544
TB (mg/dL)	1.25 ± 0.84	1.27 ± 1.1	1.24 ± 0.73	0.898
INR	1.21 ± 0.13	1.15 ± 0.11	1.23 ± 0.13	0.081
LS (kPa)	36.03 ± 19.78	30.27 ± 21.78	38.3 ± 18.8	0.219
SS (kPa)	46.76 ± 16.5	35.52 ± 15.09	51.19 ± 15.03	0.003*

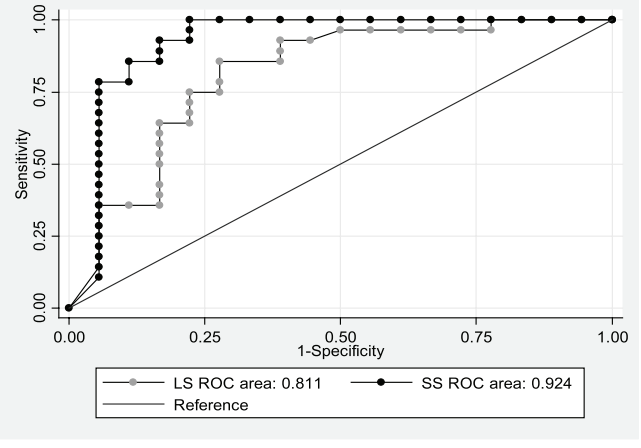

Figure 2. Receiver operating characteristic for Spleen stiffness (SS) and Liver stiffness (LS) for predicting the presence of EVs.

(51.19 vs. 35.52 kPa, p= 0.003), there was no significant difference in the mean LS (38.3 vs. 30.27 kPa, p= 0.2) between patients with and without PHG (Table 3).

SS and LS measurements in predicting the presence and the grading of EV

The LS value higher than 24.5 kPa and the AUROC value of 0.81 were shown to the Se of 85.71%, Sp of 72.22%, PPV of 82.8%, NPV of 76.5%, and diagnostic accuracy of 80.43% in predicting the presence of EV (Figure 2 and Table 4). However, LS could not differentiate patients with small varices (F1) from those with large varices (F2 and F3) (42.69 vs. 41.89 kPa, p= 0.9) (Table 5).

The SS cutoff value of 36.3 kPa with the AUROC value of 0.92 were shown to the Se of 100%, Sp of 72.22 %, PPV of 84.8%, NPV of 100%, and diagnostic accuracy of 89.13% for predicting the presence of EV (Figure 2 and Table 4). Similarly for LS, SS was not significantly higher in patients who had large varices (59.12 vs. 51.82 kPa, p = 0.096) (Table 5). Combining LS + SS ≥ (24.5 kPa + 36.3 kPa) had Se of 100%, Sp of 66.7%, PPV of 82.4%, NPV of 100%, and diagnostic accuracy of 87% for predicting the presence of EV (Table 4).

Table 4. SS and LS for predicting the presence of EVs.

	N	ROC Area	Cut off	Sensitivity	Specificity	LR+	LR-	PPV	NPV	Accuracy
LS (kPa)	46	0.8105	≥24.5	85.71%	72.22%	3.086	0.198	82.8%	76.5%	80.43%
SS (kPa)	46	0.9236	≥36.3	100%	72.22%	3.6	0	84.8%	100%	89.13%
LS+SS	46		≥60.8	100%	66.7%	3	0	82.4%	100%	87%

Table 5. Characteristics of patients with small (F1) and large (F2 and F3) EVs.

	EV (n=28)	Small EV (n=13)	Large EV (n=15)	*p*-value
Age	51.61 ± 9.79	46.92 ± 8.62	55.67 ± 9.12	0.015
Gender				
- Male	24 (85.7%)	12 (92.3%)	12 (80.0%)	
- Female	4 (14.3%)	1 (7.7%)	3 (20.0%)	
BMI	22.2 ± 1.87	22.43 ± 1.48	22 ± 2.18	0.553
Cause				
- Alcohol	16 (57.1%)	9 (69.2%)	7 (46.7%)	
- CHB	2 (7.1%)	0 (.0%)	2 (13.3%)	
- CHC	7 (25%)	3 (23.1%)	4 (26.7%)	
- NASH	3 (10.7%)	1 (7.7%)	2 (13.3%)	
CTP				
- A	10 (35.7%)	4 (30.8%)	6 (40.0%)	
- B	18 (64.3%)	9 (69.2%)	9 (60.0%)	
Alb (mg/dL)	3.24 ± 0.53	3.35 ± 0.53	3.13 ± 0.51	0.276
Plt (10^9/L)	109.07 ± 27.15	119.46 ± 15.65	100.07 ± 32.01	0.058
AST (IU/L)	63.04 ± 31.22	62.62 ± 30.52	63.4 ± 32.88	0.949
ALT (IU/L)	40.25 ± 15.74	39.54 ± 10.33	40.87 ± 19.63	0.829
TB (mg/dL)	1.36 ± 0.77	1.45 ± 0.96	1.29 ± 0.59	0.590
LS (kPa)	42.26 ± 19.82	42.69 ± 19.33	41.89 ± 20.91	0.918
SS (kPa)	55.73 ± 11.56	51.82 ± 12.81	59.12 ± 9.52	0.096

SS measurements in predicting the presence and grading of PHG

The SS cutoff value 32.3 kPa with the AUROC value of 0.79 had Se of 90.9%, Sp of 53.85%, PPV of 83.3%, NPV of 70%, and diagnostic accuracy of 80.43% for predicting the presence of PHG (Figure 3 and Table 6). SS was not significantly higher in patients with moderate to severe PHG compared to those with mild PHG (54.69 vs. 50.25 kPa, $p = 0.49$).

While neither the presence nor the grading of PHG could be differentiated by LS, combining LS + SS ≥ (19.5 kPa + 32.3 kPa) had Se of 93.9%, Sp of 53.8%, PPV of 83.8%, NPV of 77.8%, and diagnostic accuracy of 82.6%, which were higher than using SS alone in predicting the presence of PHG (Table 6).

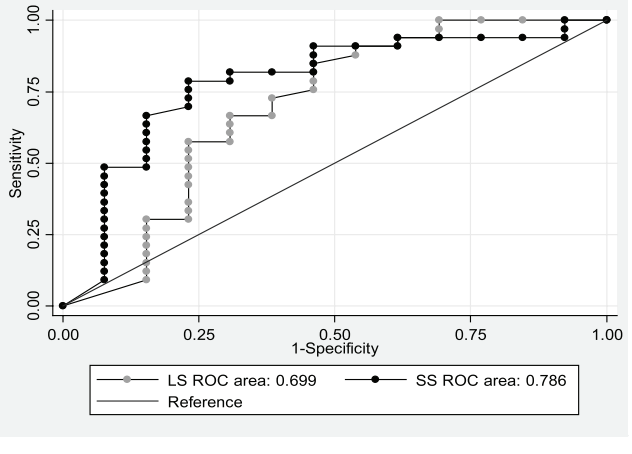

Figure 3. Receiver operating characteristic for Spleen stiffness (SS) and Liver stiffness (LS) for predicting the presence of PHG.

Table 6. SS and LS for predicting the presence of PHG.

	N	ROC Area	Cut off	Sensitivity	Specificity	LR+	LR-	PPV	NPV	Accuracy
LS (kPa)	46	0.6993	≥19.5	93.94%	38.46%	1.5265	0.1576	79.5%	71.4%	78.26%
SS (kPa)	46	0.7855	≥32.3	90.91%	53.85%	1.9697	0.1688	83.3%	70%	80.43%
LS+SS	46		≥51.8	93.9%	53.8%	2.04	0.113	83.8%	77.8%	82.6%

DISCUSSION

To date, upper GI endoscopy is considered the standard of care in patients with liver cirrhosis. Alternative noninvasive markers for assessment of portal hypertension, the severity of disease and the presence of its complications are growing issues. Splenomegaly is a common finding in patients with cirrhosis and noncirrhotic PHT and a consequence of vascular congestion, increased portal pressure, augments resistance to splenic vein outflow, and increases angiogenesis and fibrogenesis[10]. However, no relationship is noted between the degree of PHT and the size of esophageal varices[15,16]. Because of multiple histopathologic changes evolving towards diffuse fibrosis of the spleen, the increment in splenic size should correlate with changes in the density of the spleen. Such physical changes may be quantifiable by elastography. In recent studies, measurement of SS using transient elastography was shown to be a useful tool for grading chronic liver disease and for predicting the presence of EV in liver cirrhosis patients. In studies by Stefanescu *et al*[11], SS as measured by FibroScan(r) was significantly higher in patients with EV compared with those without (63.7 kPa vs. 47.8 kPa, $p = 0.001$), and SS value > 46.4 kPa could predict EV with a diagnostic accuracy of 81 %, which was higher than the LS estimation (>28 kPa; diagnostic accuracy,72%). However, SS could not predict the grade of EV. Similar results were noted by Sharma *et al*[17], who found that the cutoff value of 40.8 kPa for SS could predict EV with Se of 94 % and with diagnostic accuracy of 89 %, comparable with LS. Furthermore, SS was higher in patients with large varices compared with patients with small varices (56 kPa vs. 49 kPa, $p= 0.001$). In these previous studies, the predictability and the different cutoff values of SS varied. The aim of the present study was to determine the performance and the utility of SS in predicting EV and PHG in cirrhotic patients at our institution.

In our study, SS was significantly higher in patients with EV. Using a cutoff value of 36.3 kPa, SS could predict EV with Se of 100 %, Sp of 72% and diagnostic accuracy of 89.13%, which were higher than in the case of LS. However, SS was not significantly higher in patients with large varices compared with patients with small varices (59.1 kPa vs. 51.8 kPa, $p = 0.096$). If the cutoff SS value 47.9 kPa was used, the Se was 93.3%, but the Sp was low at 53.8% and lacking in diagnostic accuracy (75%) for differentiating small and large EV. In combination with LS, the Se or the Sp for predicting the presence of EV did not increase. Additionally, SS was significant higher in patients with PHG compared with patients without, and the cutoff value of 32.3 kPa could predict PHG with Se of 90.9 %, Sp of 53.8% and diagnostic accuracy of 80.4%. Although LS could not predict PHG, the sensitivity and the diagnostic accuracy of predicting the presence of PHG increased when using a combination of SS and LS. Overall, as with other published studies[11,12,17], SS appeared better in predicting the presence of EV. Combining of SS and LS did not yield a better performance than SS alone. SS could not differentiate the grading of EV, however, although it could predict the presence but not the grade of PHG which was better predicted using a combination of SS and LS.

Twenty-two of patients were excluded from analysis in this study due to failure of SS measurement. The failure rate was higher than in previous studies, (11.5-13%)[11,12,17]. High BMI was an independent factor for failure of valid SS measurement in recent studies[11,12]. In our study, there was no significant difference of BMI in both groups, however. This suggested that there were other relevant factors rather than BMI for a successful access to the spleen.

Another issue is whether SS and LS values vary with the etiology of liver disease. In previous studies with specific cirrhosis etiology, such as Colecchia A et al (41.3 kPa, HCV cirrhosis) and Stefanescu *et al* (46.4 kPa, HCV and alcohol related cirrhosis)[11,12], different out-off values were noted for differing cirrhosis

etiology therefore, a certain cutoff value might not be universally applicable for all cirrhotic patients. Differents cutoff values may be required for different causes of cirrhosis and PHT. In another recent study, however, no difference in SS was shown in patients with EV in the alcoholic and the non-alcoholic cirrhosis groups[17]. In our study, cirrhotic patients without selective etiology were enrolled. The utility of SS and LS for different causes of cirrhosis should be investigated further. Nevertheless, measurement of SS should be considered in liver cirrhosis patients because of its usefulness in predicting the presence of EV and PHG. This non-invasive procedure may help physicians in the evaluation of cirrhotic patients.

There were several limitations in our study. First, because of the small number of cases, the results may not be applicable to other patient populations. Second, interobserver variation in endoscopy findings regarding the presence and the grading of EVs and PHG could not be entirely excluded. Third, there was a high failure rate of SS measurement compared with recent studies. Failure rate is an area of concern and should be further evaluated.

Conclusion

SS could predict with satisfactory diagnostic accuracy the presence but not the grading of EV and PHG in liver cirrhosis patients. SS as a non-invasive test may help to identify patients at risk of having EV and PHG.

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