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A study on spleen transient elastography in predicting the degree of esophageal varices and bleeding

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Abstract

This study aims to investigate the value and determine the accuracy of spleen stiffness in predicting the degree of esophageal varices and bleeding in patients with liver cirrhosis.

The age, gender, liver stiffness, spleen stiffness, and gastroscopy results of 124 inpatients or outpatients with liver cirrhosis and healthy volunteers, who underwent both gastroscopy and FibroScan testing in the fasting state, were retrospectively analyzed. According to the gastroscopy results, the patients and healthy volunteers were divided into six groups: varicose bleeding, severe varices, moderate varices, mild varices, no varices, and healthy control group. Then, the receiver operating characteristic curves were drawn, and the corresponding area under each curve was calculated and evaluated to predict the severity of varices based on the relevance of the area and its parameters.

The area under the receiver operating characteristic curve of liver stiffness and spleen stiffness for predicting severe and moderate varices in the bleeding group was 0.955 and 0.989, respectively. The cut-off values were 29.6 kPa and 45.5 kPa, respectively. The area under the receiver operating characteristic curve of liver stiffness for predicting varicose bleeding was 0.860 (95% CI: 0.789–0.931). The liver stiffness cut-off value for predicting varicose bleeding was 33.2 kPa, with a specificity and sensitivity of 66.02% and 95.24%, respectively. The area under the receiver operating characteristic curve of spleen stiffness for predicting varicose bleeding was 0.923 (95% CI: 0.875–0.971). A spleen stiffness cut-off value of 55.2 kPa had a sensitivity and specificity of 90.48% and 86.41%, respectively.

Spleen stiffness can predict the degree of esophageal varices and bleeding in liver cirrhosis patients, and has good predictive accuracy.

Abbreviations: AUROC = area under the receiver operating characteristic curve, EV = esophageal varices, EVB = esophageal varicose bleeding, FS = FibroScan, H&E = hematoxylin and eosin, HVPG = hepatic venous pressure gradient, kPa = kilopascal, LS = liver stiffness, MiEV = mild esophageal varices, MoEV = moderate esophageal varices, NEV = none esophageal varices, NO = nitric oxide, OR = odds ratio, ROC = receiver operating characteristic, SEV = severe esophageal varices, SR = success rate, SS = spleen stiffness, TIPS = transjugular intrahepatic portosystemic shunt, VCTE = vibration control technology.

Keywords: cirrhosis, esophageal varices, spleen stiffness, varicose bleeding

1. Introduction

Esophageal variceal bleeding is one of the most dreaded complications of cirrhosis due to its high mortality. Esophageal varices are present at diagnosis in approximately 50% of cirrhotic patients. Patients of cirrhosis without varices develop this at a rate of 8% per year, while patients with small varices develop large varices at a rate of 8% per year. Variceal hemorrhage occurs at a yearly rate of 5%–15%.[1] First variceal hemorrhage occurs at an annual rate of approximately 15%, and late rebleeding occurs in approximately 60% of untreated patients, in which most occurs within 1 to 2 years of the index hemorrhage.[2,3] Although bleeding from esophageal varices spontaneously ceases in up to 40% of patients, it remains to be associated with a mortality of at least 20% at six weeks.[4–6] At present, mortality from an episode of variceal hemorrhage is lower, when compared to two decades ago, which is due to significant improvements in therapy. However, it continues to carry a significant mortality of 7%–15%.[7–10] Therefore, the early diagnosis and forecast evaluation of the degree of varices before the first hemorrhage is very crucial.

At present, the main methods for monitoring the development of esophageal varices (EV) are esophagogastroduodenoscopy and hepatic venous pressure gradient (HVPG). However, these cannot be widely used in clinical trials due to certain invasive characteristics, high clinical operation cost, and poor patient compliance. Hence, new noninvasive, low cost detective methods that can be routinely used in the diagnosis of EV and hemorrhage, the monitoring development of diseases, and the forecasting of risk factors for varicose veins needs to be developed.

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2. Materials and methods

2.1. Main materials

2.1.1. Esophagogastroduodenoscopy. Olympus 260 (Olympus, Japan).

2.1.2. Transient elastography. FibroScan 502 (Echosens, France).

2.1.3. Color Doppler ultrasound. HI Vision Preirus (Hitachi, Japan).

2.2. Experimental method

2.2.1. Object of study. A total of 124 cirrhosis inpatients or outpatients and healthy volunteers, who underwent liver stiffness (LS) and spleen stiffness (SS) by FibroScan (FS), and esophagogastroduodenoscopy in the non-fasting state in the Sixth People's Hospital, Dalian from January 1, 2012 to November 1, 2017, were included into the study. This study was approved by the Ethics Committee of the Sixth People's Hospital, Dalian, China. All patients and volunteers provided a signed informed consent. Among these 124 subjects, 22 subjects were healthy volunteers, while 102 subjects were patients with cirrhosis. Furthermore, among these 124 subjects, 98 subjects were male, while 26 subjects were female. The diagnostic criteria for esophageal varices were based on the classification criteria for esophageal varices under endoscopy formulated in 2015 in China. The criteria were as follows:

(1) mild: straight or slightly tortuous esophageal varices without red signs;
(2) moderate: esophageal varices that were straight or slightly tortuous, with red signs, or esophageal varices with snake or tortuous bulges, but without red signs;
(3) severe: esophageal varices that were serpentine or tortuous, and have red signs, or esophageal varices that were bead-like, nodular, or nodular, regardless of whether it is red or not.

Among these 124 subjects, 21 subjects were patients with esophageal varicose bleeding (EVB), 19 subjects were patients with severe esophageal varices (SEV), 22 subjects were patients with moderate esophageal varices (MoEV), 22 subjects were patients with mild esophageal varices (MiEV), 18 subjects were patients with none esophageal varices (NEV), and 22 subjects were healthy subjects assigned as controls. The diagnosis of EV under endoscopy, LS, and SS were recorded. The age of subjects with EVB ranged within 36 to 69 years old, with a mean age of 55 years old. The age of subjects with SEV ranged within 35 to 81 years old, with a mean age of 56.8 years old. The age of subjects with MoEV ranged within 33 to 78 years old, with a mean age of 52.6. The age of subjects with MiEV ranged within 33 to 83 years old, with a mean age of 52.3 years old. The age of subjects with NEV ranged within 21 to 84 years old, with a mean age of 53.2 years old. The age of controls ranged within 36 to 81 years old, with a mean age of 54.0 years old.

2.2.2. Operation method for liver transient elastography. Measurements were performed on the area of the right side of the 7–9 rib gap from the anterior axillary line to the midaxillary line. Patients were placed in the dorsal decubitus position with the right arm in the maximal abduction. The operator placed the probe vertically on the skin surface. With the assistance of ultrasound time-motion imaging, the operator located a liver section that was at least 6 cm thick, and was free of large vascular structures. After the measurement area was located, the operator pressed the probe button to start an acquisition. The measurement depth ranged within 25 to 65 mm below the skin surface. Ten successful measurements were performed on each patient. The success rate (SR) was calculated as the ratio of the number of successful measurements over the total number of acquisitions. The results were expressed in kilopascal (kPa). The median value of the successful measurements was kept as a representative of LS. Merely LS measurements obtained with at least 10 successful measurements, a SR of at least 60%, and an IQR of <30% (IQR, which is the interquartile range interval, is the difference between the 75th and 25th percentile, and is essentially the range of the middle 50% of the data) were considered reliable. The LS results are presented in Figure 1.

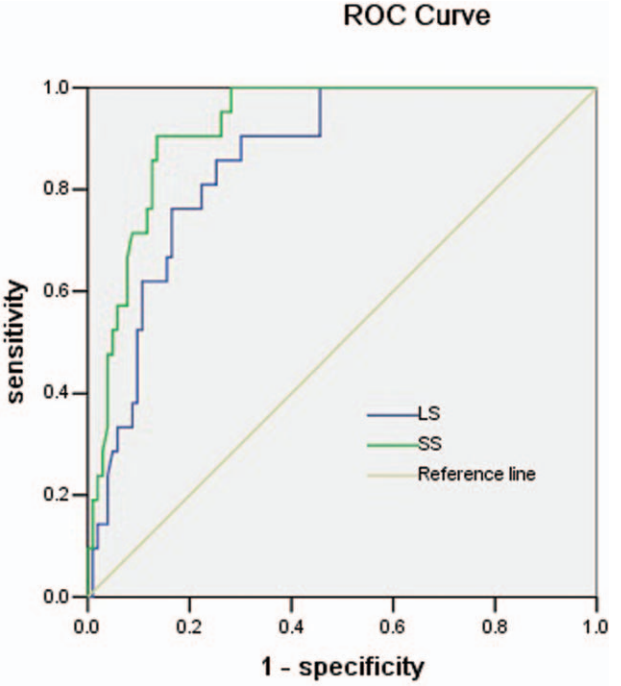

Figure 1. The ROC of LS and SS for prediction in the EVB group. EVB = esophageal varicose bleeding, LS = liver stiffness, ROC = receiver operating characteristic, SS = spleen stiffness,

2.2.3. Operation method of the spleen transient elastography. The patients were placed in the dorsal decubitus position with the left arm in maximal abduction, and the position of the probe was placed on the 9–11 rib gap of the left posterior axillary line. The operation method of the spleen transient elastography was the same as that in the liver transient elastography. The probe was perpendicular to the surface of the skin. According to TM, a model of the ultrasonic image of the FibroScan instrument was established to check the right location. Each patient was measured for 10 times, and the median was taken as the final result, which was expressed as a flexible value (FS).

2.2.4. Inclusion criteria. Inclusion criteria: patient who were ≥18 years old; patients with liver cirrhosis; patients who provided a signed informed consent.

2.2.5. Exclusion criteria. Exclusion criteria: patients who received blood transfusion, had esophageal variceal bleeding caused by non-cirrhosis, or had isolated gastric variceal tumors or hepatic carcinoma; patients who underwent hepatic intervention,

splenic intervention, portosystemic shunt or transjugular intrahepatic portosystemic shunt (TIPS); patients with perihepatic, perisplenic, or abdominal ascites; patients who were pregnant or had implanted heart pacemakers.

2.3. Statistical method

The distribution of continuous data was tested by Shapiro–Wilk test. The categorical variables were compared using X^2-test. The mean variables between two groups were compared using Student's *t*-test, and the mean variables among multiple-groups were compared using one-way analysis of variance. The area under the receiver operating characteristic curve (AUROC) was used to select the parameter that revealed a good discriminative power for predicting the presence of EV. In addition, the receiver operating characteristic (ROC) curve was used to determine the cut-off value with the best sensitivity and specificity. Data were presented as the mean ± standard deviation, and each odds ratio (OR) and AUROC curve were presented together with its 95% confidence interval (95% CI). A two-sided $P < .05$ was considered statistically significant for all analyses. Data were analyzed using SPSS 13.0.

3. Results

3.1. Comparison of all parameters among all groups

In our study, the continuous variables were normally distributed. Therefore, we expressed the numerous variables as mean ± SD. Table 1 shows the main characteristics of these six groups of patients according to the presence of EV. There were no significant differences among these six groups with regard to age and gender. Patients with EVB had significantly higher LS and SS, when compared to healthy patients. Furthermore, there were no significant differences between the MoEV group and SEV group with regard to LS and SS ($P = .297$). Moreover, there were no significant differences between the MiEV group and NEV group with regard to LS and SS ($P = 1.0$). In addition, the figure for LS and SS were not in positive correlation with the varices in the seven cases.

3.2. Comparison of LS and SS among the four recombined groups

According to the results in Table 1, six groups of LS and SS were recombined into four groups as follows: patients with esophageal varicose bleeding (EVB group), patients with moderate or severe esophageal varices (MoEV+SEV group), patients with no or mild esophageal varices (NEV+MiEV group), and healthy controls group. The differences were statistically significant among these four groups with regard to LS and SS. Patients with EVB had significantly higher LS and SS, when compared to other patients (Table 2).

3.3. Comparison of ROCs in predicting liver stiffness and spleen stiffness in the varices bleeding group

In the ROC curve (Fig. 1), the AUROC for the LS prediction of EVB was 0.860 (Table 3; 95% CI: 0.789–0.931) in the present study population, which was lower than for SS (AUROC = 0.923; 95% CI: 0.875–0.971). Therefore, SS has a better discriminative power for predicting the presence of EVB, when compared to LS, in the present study population. Finally, the ROC curves were used to assess the cut-off values for the LS and SS scores with the best sensitivity and specificity for predicting the presence of EVB. A cut-off value of 55.2 kPa had a sensitivity and specificity of 90.48% and 86.41%, respectively, a positive likelihood ratio of 6.66, and a negative likelihood ratio of 0.11.

4. Discussion

The liver is supplied by two sets of blood vascular systems: portal veins and hepatic veins. Furthermore, the spleen is supplied by the splenic vein system. Anatomically, the splenic vein and portal vein communicate with each other. In theory, when it is in the portal hypertension state, hyperdynamic circulation in the spleen is more obvious than that in the liver. Therefore, the value of SS is more sensitive than LS. Based on the principle of FibroScan (FS), and its practice and clinical significance in predicting liver fibrosis by LS, researchers found that the application of FS enabled the monitoring of SS and prediction of the degree of splenic fibrosis,

Table 1

The comparison of all parameters among all groups ($\bar{x} \pm s$).

Parameters	Varicose bleeding group	Severe varicose group	Moderate varicose group	Mild varicose group	No varicose group	Healthy controls group
Gender (male, %)	18 (85.7)*	16 (84.2)	17 (77.3)	18 (81.8)	13 (72.2)	16 (72.7)
Age (year)	55 ± 11.6*	56.8 ± 10.3	52.6 ± 13.0	52.3 ± 9.5	53.2 ± 10.1	54.0 ± 9.6
Liver stiffness (kPa)	44.3 ± 11.7	37.4 ± 12.8 †	34.7 ± 7.0	21.5 ± 6.5 ‡	20.2 ± 6.1	5.6 ± 1.6
Spleen stiffness (kPa)	61.4 ± 6.2	51.6.1 ± 6.5 §	48.5 ± 4.9	34.5 ± 5.3 ¶	32.4 ± 8.0	21.5 ± 4.7

* Compared with each group, $P > .05$.
† Compared with moderate varicose group, $P = .297$.
‡ Compared with no varicose group, $P = 1.0$.
§ Compared among the rest of each groups, $P < .05$.
¶ compared among the rest of each groups, $P < .05$.

Table 2

The comparison of LS and SS among four groups.

Prediction models	EVB group	MoEV+SEV group	NEV+MiEV group	Healthy controls group	*P* value
Liver stiffness (kPa)	44.34 ± 11.65	36.24 ± 10.69	20.91 ± 6.29	5.58 ± 1.61	<0.001
Spleen stiffness (kPa)	61.42 ± 6.21	50.95 ± 7.45	34.19 ± 7.00	21.51 ± 4.69	<0.001

EVB = esophageal varicose bleeding, MoEV = moderate esophageal varices, NEV = none esophageal varices, SEV = severe esophageal varices.

Table 3

The comparison of ROC of liver stiffness and spleen stiffness prediction of the varices bleeding group.

Prediction models	AUC	95% CI	Z statistic	Criterion (kPa)	Sensitivity (%)	95% CI	Specificity (%)	95% CI	+LR	−LR
Liver stiffness	0.860	0.789–0.931	9.935	>33.2	95.24	76.2–99.9	66.02	56.0–75.1	2.80	0.072
Spleen stiffness	0.923	0.875–0.971	17.239	>55.2	90.48	69.6–98.8	86.41	78.2–92.4	6.66	0.11

AUC = area under the curve, CI = confidence interval, LR = likelihood ratio.

in order to forecast the extent of portal hypertension and indirectly predict the EGV level. Groshar and other experts indicated that the increase in splenic volume is a sensitive indicator for the diagnosis of liver cirrhosis.[11–13]

Some scholars have found that the SS in patients with liver cirrhosis is higher than that in non-liver cirrhosis patients, and SS in varicocele patients is higher than that in non-varicocele patients.[14] Stefanescu et al confirmed these results. When the threshold was 52.5 kpa, the AUROC was 0.74. When compared with LS, they found that SS had higher diagnostic accuracy.[15] Furthermore, an academic study revealed that SS has a better value for predicting the level of EV, when compared with Plt/S-D.[16,17] The systemic review conducted by Singh et al revealed that the sensibility of EV was 78%, the specificity was 76%, and the diagnostic OR was 19.3. Moreover, according to a meta-analysis, sensitivity was 81% and specificity was 66%. Due to elasticity imaging techniques and different study sites, there was significant heterogeneity. In the mean time, there was disease spectrum bias and disease progression of bias. Therefore, Singh considered that existing spleen hardness measurement technology limits the accuracy for predicting EV according to SS, and thereby limits the extensive development of technology in clinic.[18] Nevertheless, in recent years, an increasing number of scholars attempted to study and apply SS to predict the occurrence and development of EVG and its appraised value of bleeding, and this method has a promising future.[19–23]

Compared to the invasive liver biopsy method, the measurement of hardness of the liver (LS) according to FS can relatively reflect the degree of fibrosis in 95% of patients with liver disease. Due to its high accuracy, repeatability, and patient compliance, this has received more and more academic attention. The principle for measuring LS and SS according to FS was the use of transient elastography vibration control technology (VCTE) to evaluate the hardness value of homogeneous organs in thousands of units of kPA. This means that the higher the elastic numbers were, the larger the hardness value in the organ tissue becomes. Some scholars have found that when LS was lower than 19 kPa, this can predict the presence of moderate-to-severe esophageal and gastric varices. When the threshold of LS was 27.5–35.0 kPa, moderate-to-severe varicose veins can be forecasted, and the threshold of variceal bleeding was 62.7 kPa.[24] Wang and other experts found that the critical value of predicting esophageal and gastric varices was 13.4 kpa (the AUROC was 0.85), while the critical value of severe varicose veins was 14.6 kpa (the AUROC was 0.83).[25] LS is the best nonintrusive check for patients with clear clinically significant portal hypertension.[26] At present, with the deepening of research, researchers found that LS numerical results are dictated by gender, body size, change in inflammation, and necrosis. Hence, the application of LS in predicting liver fibrosis has been limited, and is not a good predictor for liver disease progression in liver fibrosis.[27,28]

Among all the collected cases, it was found that the figure of LS and SS was not in positive correlation with the varices in the seven cases. Hence, there may be certain differences among SS values previously measured and those that were measured after the endoscopic treatment. Therefore, the investigators advocate that when SS and LS are measured, patients not treated with endoscopy and patients who underwent endoscopic treatment should be clearly distinguished. In addition, further research is required to clarify the impact of SS values before and after endoscopic treatment. In accordance with the above theory, it was considered whether all the influence factors of portal pressure would affect the high and low values of LS and SS, such as the reduction of medicines, blood transfusion treatment for portal vein pressure, and endoscopic therapy. After removing the influence factors for portal pressure, it was found that SS was relative to LS, and has a higher predictive value in terms of the moderate or severe varicose veins in the hemorrhage group and varicose veins.[29] However, these finding remains controversial,[30,31] as presented in Tables 2 and 3.[32,33] In the future, cases treated by endoscopic hemostasis should be compared with cases that did not receive endoscopic hemostatic treatment, in order to further study the predictive accuracy of SS, and the sensitivity of EV and bleeding.

Limitations: First, the present study is a single-center study with a small sample size, and further multi-center trials with a large sample size are still needed. Second, the present study only included Chinese patients, and there was no worldwide cohort study. Third, the correlation between liver and spleen stiffness remains unknown, and requires further research.

5. Conclusion

SS can be utilized to predict the degree of EV in patients with cirrhosis and risk of EV bleeding, which has high predictive accuracy. In the future, the correlation between predicting extent of SS and bleeding of EV can be further studied from a large sample of patients in multi-centers. Moreover, further studies should be conducted to determine whether pre- and post-endoscopic hemostasis treatment has an effect on the measured values of SS.

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