Title page

1) Title: Predict esophageal varices via routine trans-abdominal ultrasound: a design of classification analysis model.

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5) A short running title: Predict EV via routine TUS
Abstract:

**Background and Aims:** Upper gastrointestinal endoscopy remains the gold standard for diagnosis of esophageal varices. Trans-abdominal ultrasound, as a noninvasive routine examination for the follow-up of cirrhosis patient, is safe, cheap, easy to perform, and plays an important role. In this study, we attempt to design a practical classification analysis model to predict esophageal varices via ultrasound. **Methods:** Compared with endoscopy, the ultrasound qualitative signs (lower esophageal Doppler signals, left gastric vein hepatofugal flow, paraumbilical vein recanalization) and quantitative parameters (spleen diameter, spleen vein diameter, portal vein diameter, and portal vein velocity) have been evaluated in 286 cirrhosis patients. **Results:** The classification analysis model is designed as that: the patients are defined with esophageal varices high risk, who with any ultrasound qualitative signs or who with spleen diameter greater than 162mm without qualitative parameters. The sensitivity for detecting esophageal varices is **97.5%** and the specificity is **82.6%**, while the positive predictive value is **96.7%**, negative predictive value is **83.4%** and the omission diagnostic rate is **2.5%**. **Conclusions:** This classification analysis model design includes ultrasound qualitative signs and spleen diameter, which can be detected easily via routine ultrasound without other auxiliary. The classification analysis model is useful in detecting esophageal varices, which may be a supplement for predicting of esophageal varices, and reduce the frequency of endoscopy in the follow-up of cirrhosis patients.

**Keywords:** Portal hypertension; Esophageal varices; Ultrasound; Diagnosis.
**Introduction**

Esophageal varices (EV) are the most important portosystemic collaterals because their rupture results in esophageal varices bleeding. Upper gastrointestinal endoscopy remains the gold standard for diagnosis of EV. A number of practice guidelines recommend periodic endoscopic examination of patients with cirrhosis for varices [1, 2]. However, less than 50% of cirrhotic patients have varices at the screening endoscopy, which implies a considerable burden for endoscopy units and an increased number of unpleasant procedures for patients. Even though researchers have evaluated many possible noninvasive markers of EV [3-7], the clinical value remains controversial.

Trans-abdominal ultrasound (TUS), as a noninvasive routine examination for the follow-up of cirrhosis patient, is safe, cheap, and easy to perform. But, the diagnostic value of TUS in detecting EV is still considered unsatisfactory. For example, splenomegaly has high sensitivity but low specificity in detecting PH or EV; on the other hand, abdominal portosystemic collaterals have low sensitivity and high specificity. Many qualitative parameters are significant correlations with EV, and can be easily detected via TUS in routine examination without other auxiliary, such as lower esophageal Doppler signals (LEDS), left gastric vein (or coronary vein) hepatofugal flow (LGVHF), paraumbilical vein recanalization (PUVR), and so on.

In this study, we attempted to design a practical classification analysis model (CAM) to predict EV and improve the predictive value of TUS.
Patients and Methods

Design of the CAM

The qualitative signs (LEDS, LGVHF, and PUV) and quantitative parameters (spleen diameter, spleen vein diameter, portal vein diameter, and portal vein velocity) were evaluated in all patients.

Firstly, the parallel test of the qualitative signs was performed in all patients: the patients with any qualitative signs were defined as EV high risk and classified as Group 1. The patients without the qualitative signs were classified as Group 2.

Secondly, the correlation between quantitative parameters and EV diagnosed by endoscopy was analyzed in Group 2. The patients in Group 2 with EV high risk were defined according to the cut-off values of quantitative parameters.

Lastly, all patients with EV high risk, defined via TUS, were accumulated in both Group 1 and Group 2, and the data were analyzed.

Patients:

This study population consisted of 286 cirrhosis patients caused by HBV (195 men and 91 women, median age 57, range 30-78 years). The patients were diagnosed based on the standard clinical, imaging, and biochemical parameters. The patients were recruited consecutively in our hospital from August, 2012 to January, 2015. The exclusion criteria included portal or splenic vein thrombosis, previous operative treatment for portal hypertension, previous endoscopic sclerosis or band ligation of EV. The study was approved by the Institutional Ethical Committee of our hospital and was conducted according to the principles of the Declaration of Helsinki. The nature of study was explained to patients, each...
of them provided written informed consent before the study.

**Gastroesophageal endoscopy:**

Gastroesophageal endoscopy was performed by a single doctor (D-R K) using an Olympus GIF-XQ 260 video endoscope (Olympus, Beijing, China), and EV was classified as present or absent according to the same criteria: EV was present when there were elevated veins above the esophageal mucosal surface regardless size or shape.

**Ultrasound:**

Ultrasound examination was performed using a GE Logiq 7 system (General Electric Healthcare Medical Systems, Milwaukee, WI, United States) with 4C convex-arrayed transducer (3-6 MHz) and 10L linear-arrayed transducer (5-10 MHz). All subjects fasted overnight before TUS examination and examined by a single doctor (C-X Z). To evaluate the reproducibility in classifying TUS qualitative parameters and measuring of TUS quantitative parameters, all subjects were examined by another doctor (L W) again. Both doctors were blinded to the findings on endoscopy, and the second doctor (L W) was also blinded to the TUS findings done by the first doctor (C-X Z).

First, the qualitative parameters were evaluated via TUS for all patients. The Doppler US settings were optimized for slow blood flow detection, which included the lowest wall filter and the highest Doppler gain possible without flash artifacts and the lowest possible pulse repetition frequency without aliasing. (1) LEDs: After visualization of the lower esophagus under normal B mode scanning, color Doppler flow imaging (CDFI) was used to detect LEDs under esophageal resting. If necessary, the subjects were asked to swallow a bolus of water, which can improve the display rate of LEDs[8]. To show the lower esophagus
clearly, all patients were examined in the supine position and right anterior oblique.  ⑵PUVR: For each patient, the ligamentum teres was identified, and then CDFI was attempted with two probes of convex-arrayed transducer and linear-arrayed transducer. If there was hepatofugal venous blood flow in the ligamentum teres, it would be defined as PUVR.  ⑶LGVHF: The left gastric vein was identified as a tubular structure arising from the splenic or portal vein, coursing cephalad within the gastrohepatic ligament toward the esophagogastric junction. CDFI was used to identify whether there has LGVHF.

Then, quantitative parameters were evaluated via TUS: ⑴Portal vein velocity was measured in the mid-portion, where the hepatic artery crosses the portal vein. The angle between the long axis of the portal vein and the Doppler beam was less than 60. ⑵Portal vein diameter was measured in the longitudinal section, at the exact site in the portal vein mid-portion. ⑶Spleen diameter was the maximum length of the poles on oblique subcostal scans. ⑷Spleen vein diameter was measured in the longitudinal section at the hilum of spleen.

**Statistical analysis**

Statistical analysis was performed with SPSS 15.0 software. Comparisons between groups were performed using the chi-square test for qualitative data and the Student t test for quantitative data. A \( P \)-value of less than 0.05 was considered to indicate a significant difference.
Results

Among these 286 patients, 116 were Child-Pugh class A (40.6%), 135 were class B (47.2%) and 35 were class C (12.2%), and 121 patients with ascites (42.3%). Lower esophagus can be clearly displayed in 258 cases (90.2%) by TUS, whereas 28 patients (9.8%) did not show clearly due to massive ascites, obesity or liver atrophy. On the whole, LEDS were detected in 152 of 286 patients (53.1%) by TUS, which are expressed as short cord-like or continuous color signals in the esophageal wall and the lumen (Fig 1 A). LGVHF were detected in 78 of 286 patients (27.3%) by TUS (Fig 1 B), whereas 208 patients didn’t have LGVHF, including these patients whose LGV could not be seen clearly (80 patient, 28.0%) or patients whose LGV had hepatopetal blood flow (128 patients, 44.8%). PUVR were detected in 51 of 286 patients (17.8%), which displayed as red color hepatofugal flow in the ligamentum teres (Fig 1 C).

According to the parallel test design, there were 214 patients with these qualitative signs, without considering the numbers of these signs. These 214 patients were classified as Group 1 with EV high risk. Compared with endoscopy, 211 patients with EV in Group 1, and 3 patients didn’t have EV who have PUVR merely. Among 214 patients, 61 patients were shown with gastric varices according to endoscopy.

In addition to the 214 patients, the remaining 72 patients were classified as Group 2. The correlation between quantitative parameters and EV diagnosed by endoscopy examination was showed in table 1. The spleen diameter has the highest AUC of ROC among these parameters, and was selected to be analyzed. Among the 72 patients in group 2, 28 patients were defined with EV high risk, according to the cut-off value of 162 mm of spleen diameter,
with 23 patients were diagnosed with EV and 5 patients were without EV compared with endoscopy. And the remaining 44 patients were defined without EV high risk. However, 6 of 44 patients were diagnosed as EV by endoscopy. In addition, 8 patients in group 2 were defined with gastric varices according to endoscopy.

In this study, we developed this classification analysis model (CAM): the patient with any qualitative signs or spleen diameter greater than 162mm without qualitative parameters, were defined with EV high risk (Fig2). For the whole individuals in the present study, the patients with EV high risk evaluated by TUS and EV patients diagnosed by endoscopy were showed in table 2. This CAM has 97.5% sensitivity, 82.6% specificity, 96.7% positive predictive value, and 83.4% negative predictive value for detecting EV in whole patients and the omission diagnostic rate of EV is 2.5%.

In addition, we evaluate the predictive value of CAM in Child-Pugh class A group especially. According to this CAM, there have 85 patients with and 31 patients without EV high risk in Child-Pugh Class A group. Among these 85 patients, there have 79 patients with EV and 6 patients without EV compared with endoscopy. Among the 31 patients, there have 7 patients with EV and 24 patients without EV compared with endoscopy. So this CAM has 91.2% sensitivity, 80% specificity for predicting EV in Child-Pugh Class A group especially.

As a result, we also evaluated the predictive value of the quantitative parameters of TUS in the whole patients. As shown in table 3, these four quantitative parameters of TUS displayed difference between patients with EV and without EV. However, the sensitivity, specificity, positive predictive value and negative predictive value were too lower to evaluate EV accurately. Compared with the single parameter of TUS, this CAM showed higher value.
in predicting EV in cirrhosis patients.

Concordance of defining TUS qualitative parameters and reproducibility of spleen diameter were also analyzed. Between the two doctors, concordance in classifying TUS qualitative parameters was 98%. In addition, there was statistically significant correlation between the two doctors in spleen diameter measurement ($r=0.95; P<0.001$).

**Discussion**

To reduce the frequency of endoscopies in patients with cirrhosis, some noninvasive markers of EV (such as: spleen diameter, platelet count/spleen diameter ratio, and so on) have been evaluated, even though some promising results have been shown, the clinical value is controversial [6, 9-13]. Recently, transient elastography (Fibroscan) has been proposed as a new method to diagnosis cirrhosis or EV. Although the accuracy of elastography in diagnosing cirrhosis seems good, its discriminative ability in the prediction of EV appears inadequate [14-18].

As a noninvasive routine examination, TUS has played an important role in the follow-up of cirrhosis patients. In this study, we evaluated the predictive value of the quantitative parameters of TUS to predict the presence of EV in 286 patients. The results show that the sensitivity, specificity, positive predictive value and negative predictive value are too lower to predict EV accurately.

The ability to detect the intra-abdominal esophagus with TUS has been previously recognized. Many studies have demonstrated that TUS can provide useful information in
detecting EV by evaluating the abdominal esophagus, such as the thickness, the pattern of the esophageal wall, and the Doppler signal flow of EV [19-22]. Our previous study indicated that swallowing action can significantly improve lower esophageal EV Doppler signal display during TUS compared with the esophageal resting state, which was benefit to detect EV [8].

The display of lower esophagus and LEDS can be improved by changing the TUS inspection methods [8, 23]. So lower esophagus can be clearly displayed in 258 cases (90.2%) and LEDS were detected in 152 patients (53.1%) by TUS in this study. These 152 patients with LEDS were confirmed as EV by endoscopy at the end. It is said the LEDS was the direct reflex of EV in color Doppler model.

The diameter of LGV is too small to be measured correctly, and the accuracy and reproducibility is controversial. So we focused on the flow direction of LGV in this study.

This study showed a close relationship between LGVHF and EV. LGVHF were detected in 78 of 286 patients (27.3%) by TUS, and all 78 patients were confirmed as EV by endoscopy. PUVR were detected in 51 of 286 patients (17.8%). According to the endoscopy, 3 patients didn’t show EV, but only show PUVR.

Because of the ascites, obesity, liver atrophy, and the lower occurrence rate, the three sonographic parameters LEDS, LGVHF, and PUVR were detected in 53.1%, 27.3%, and 17.8% of the whole patients in this study, respectively. It is too lower to predict EV accurately by a single parameter.

According to the parallel test design, the patient was defined as EV high risk as long as who has any of these three qualitative signs. Our study showed that 214 patients with these qualitative signs, regardless of numbers of these signs, were defined as EV high risk.
Compared with endoscopy, 211 cases were defined with EV in these 214 patients. Even though single qualitative sign of TUS displayed low display rate, this parallel test design could get higher positive rate.

These qualitative signs showed low sensitivity, even though they displayed high specificity in predicting EV. So the correlation between quantitative parameters of TUS and EV diagnosed by endoscopy was analyzed in other 72 patients without the qualitative signs. The spleen diameter was the highest AUC of ROC among the quantitative parameters. The best cut-off value of spleen diameter was 162 mm according to ROC. With this cut-off value, 28 patients were defined with EV high risk among these 72 patients. However, 5 patients without EV were classified to EV high risk, and 6 patients were omitted diagnosed.

This CAM design included ultrasound qualitative signs and spleen diameter, which could be detected easily via routine ultrasound without other auxiliary. The significant finding in our study is that the CAM has 97.5% sensitivity, 82.6% specificity, 96.7% positive predictive value, and 83.4% negative predictive value for predicting EV in whole patients and the omission diagnostic rate of EV is 2.5%. This CAM has 91.2% sensitivity, 80% specificity for predicting EV in Child-Pugh Class A group especially.

This was a pilot study and thus existed some limitations, such as patient selection bias, because it did not include all patients with various stages of chronic liver disease and other different population and EV was present in approximately 83.9% in this study, which was higher than previous literatures. In addition, TUS qualitative parameters were likely to be more or less subjective, so the TUS setting should be unified and optimized to decrease this subjective effect. The value of CAM needed to be confirmed in prospective multicenter study.
with a broader range of patients and different etiology patients without endoscopically proven EV. In conclusion, upper gastrointestinal endoscopy remained the gold standard for diagnosis of EV. Our study indicated that this CAM might be a supplement for predicting of EV, which could reduce the frequency of endoscopy in the follow-up of cirrhosis patients.

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Potential conflict of interest: No.
References:


11. de Mattos AZ, de Mattos AA. Platelet count/spleen diameter ratio: can it replace endoscopy for the screening of esophageal varices in cirrhotic patients? *Eur J Gastroenterol Hepatol* 2012; **24**: 1113.


Fig 1. Images of qualitative parameters of TUS.

A: LEDS expressed as blue color signals in esophageal wall and lumen (white arrow); B: LGVHF shows as red color arising from portal vein (white arrow); C: PUVR displayed as red color hepatofugal flow in the ligamentum teres (white arrow).
Fig 2. The design of classification analysis model (CAM) and results (N: patient numbers).
Table 1. Correlation between quantitative parameters of TUS and EV diagnosed by endoscopy in patients without qualitative signs (N=72).

<table>
<thead>
<tr>
<th>quantitative parameters of TUS</th>
<th>Without EV (N=43)</th>
<th>With EV (N=29)</th>
<th>P-value</th>
<th>AUC of ROC curve</th>
<th>Cut-off value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spleen diameter (mm)</td>
<td>117 (74-186)</td>
<td>179 (115-260)</td>
<td>0.001</td>
<td>0.85</td>
<td>162</td>
</tr>
<tr>
<td>Spleen vein diameter (mm)</td>
<td>6.1 (4-15)</td>
<td>12.0 (7-21)</td>
<td>0.001</td>
<td>0.62</td>
<td>10.2</td>
</tr>
<tr>
<td>Portal vein diameter (mm)</td>
<td>11.5 (9-16)</td>
<td>15.6 (11-25)</td>
<td>0.004</td>
<td>0.77</td>
<td>14.3</td>
</tr>
<tr>
<td>Portal vein velocity (cm/s)</td>
<td>23.2 (15-29)</td>
<td>18.3 (12-35)</td>
<td>0.048</td>
<td>0.42</td>
<td>19.6</td>
</tr>
</tbody>
</table>
Table 2. The predictive value of TUS was analyzed compared with endoscopy in whole patients.

<table>
<thead>
<tr>
<th>Endoscopy</th>
<th>With EV</th>
<th>Without EV</th>
</tr>
</thead>
<tbody>
<tr>
<td>With EV high risk</td>
<td>234</td>
<td>8</td>
</tr>
<tr>
<td>Without EV high risk</td>
<td>6</td>
<td>38</td>
</tr>
</tbody>
</table>

Compared with endoscopy, TUS detecting EV, $r=0.632$, $P<0.001$. Sensitivity: 97.5%; Specificity: 82.6%; Positive predictive value: 96.7%; Negative predictive value 83.4%.
Table 3. The predictive value of the quantitative parameters of TUS in the whole patients (N=286).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Without EV (N=46)</th>
<th>With EV (N=240)</th>
<th>P-value</th>
<th>AUC of ROC curve</th>
<th>Cut-off value</th>
<th>sensitivity</th>
<th>specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spleen diameter (mm)</td>
<td>118 (74-186)</td>
<td>182 (115-273)</td>
<td>0.000</td>
<td>0.83</td>
<td>160</td>
<td>86%</td>
<td>75%</td>
<td>81%</td>
<td>69%</td>
</tr>
<tr>
<td>Spleen vein diameter (mm)</td>
<td>6.2 (4-15)</td>
<td>12.3 (7-24)</td>
<td>0.025</td>
<td>0.58</td>
<td>10.2</td>
<td>65%</td>
<td>72%</td>
<td>61%</td>
<td>68%</td>
</tr>
<tr>
<td>Portal vein diameter (mm)</td>
<td>11.4 (8-16)</td>
<td>15.6 (10-25)</td>
<td>0.014</td>
<td>0.81</td>
<td>14.5</td>
<td>80%</td>
<td>73%</td>
<td>77%</td>
<td>72%</td>
</tr>
<tr>
<td>Portal vein velocity (cm/s)</td>
<td>23.5 (15-29)</td>
<td>18.7 (12-41)</td>
<td>0.062</td>
<td>0.52</td>
<td>20.1</td>
<td>58%</td>
<td>61%</td>
<td>48%</td>
<td>56%</td>
</tr>
</tbody>
</table>