

# Prediction and screening of esophageal varices in cirrhotic patients using doppler US hemodynamic indices of portal system

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## Abstract

It is currently recommended that all patients with liver cirrhosis undergo upper gastrointestinal endoscopy (UGIE) to identify those who have esophageal varices (EV) that carry a high risk of bleeding and may benefit from prophylactic measures. In the future, this social and medical burden will increase due to the greater number of patients with chronic liver disease and their improved survival. The aim of this study was to assess the value of Doppler sonography for the prediction/screening of EV in cirrhotic patients. In this two-year prospective study, 50 patients with liver cirrhosis, referred to Al-Zahra hospital, were enrolled. Patients underwent detailed clinical examination, biochemistry tests (hematology, liver function tests), Gray-scale ultrasonography and Doppler sonography of hepatoportal system. Degree of esophageal varices was assessed at UGIE; Paquet's grades 0 – III were classified as group A (0-I; No or Mild EV) and group B (II-III; Moderate to severe EV). Three portal hemodynamic indices including liver vascular index, portal hypertension index, and congestive index was also measured. Degree of esophageal varices was assessed at UGIE. The relationship between the presence and degree of EVs with Doppler results were evaluated. Among 50 consecutive cirrhotic patients (41 males and 9 female, with mean age of 52.1(±16.2) year) were enrolled. 19 (38%) patients were placed in group A (No or mild EV), while 31(62%) had endoscopic evidences of moderate to severe esophageal varices (group B). Our study showed that among three portal hemodynamic indices we studied, only portal hypertension index has statistically significant correlation with degree of EVs confirmed by UGIE ( $P=0.029$ ). Doppler ROC area under the curve was not significant but was near to be ( $AUC=0.64$ ). Our data indicate that Doppler sonographic evaluations have no highly accurate predicting value for the presence of EV and its severity in patients with cirrhosis. However, we

think Doppler study can be helpful for further investigation and finding more established and unchangeable information.

## Introduction

Esophageal varix (EV) is a common major complication in patients with cirrhosis, with an estimated prevalence about 35-80%<sup>1</sup> and an annual incidence of approximately 5 % for EV formation in patients with liver cirrhosis.<sup>2,3</sup> The presence of varices correlates with the severity of liver diseases; varices are present in 30-40% of patients with compensated cirrhosis (Child-Pugh class A) and in 60-85% of patients with decompensated cirrhosis (Child-Pugh classes B and C).<sup>4,5</sup> Esophageal varices are the most common sources of bleeding in patients with cirrhosis.<sup>6</sup> It is considerable that esophageal variceal bleeding might be a lethal complication in these patients with estimated mortality rate of 20-5%.<sup>5-8</sup> Variceal bleeding occurs in approximately one third of the patients with EV, which may be repeated in up to 70% of these cases.<sup>9,10</sup> Endoscopic screening for esophageal varices is recommended in patients with newly diagnosed chronic cirrhosis, because medical treatment must be considered as soon as varices are detected to prevent bleeding.<sup>11</sup> Some recent studies have evaluated different noninvasive measures, such as capsule endoscopy, biochemical, clinical and ultrasonographic parameters to predict the presence of esophageal varices before invasive screening endoscopy.<sup>12-15</sup> Use of accurate and specific non-invasive methods may help to identify high-risk patients for esophageal varix development who can benefit from prophylactic pharmacologic and endoscopic therapies and to avoid unnecessary endoscopy in low-risk patients.<sup>16</sup> Some new studies have suggested using the ultrasonographic examination as a simple, inexpensive, accurate, and noninvasive technique. Various ultrasonographic (US) indexes, including spleen size, portal vein velocity (PVV), portal vein diameter, hepatic impedance indexes, splenic impedance indexes, and results of multi-detector computed tomographic esophagography, have been shown to be predictive of the severity of esophageal varices or risks of variceal bleeding in patients with cirrhosis.<sup>17-20</sup> However, no consistent results have been reported yet.

The purpose of our study was to assess the value of US indexes for predicting the presence of esophageal varices in patients with cirrhosis. We have used endoscopy as the reference standard.

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## Materials and Methods

We enrolled 50 of consecutive newly diagnosed cirrhotic patients who were visited at our clinic, prior to any treatment in the Al-Zahra hospital (affiliated to the Isfahan University of Medical Sciences). The diagnosis of cirrhosis was based on a liver biopsy or clinical and biochemical evaluations.

The following information was taken from each patient: age, gender, etiology of cirrhosis, onset of the disease, biochemical parameters [aspartate amino-transferase (SGOT), alanine amino-transferase (SGPT), total bilirubin, serum albumin, prothrombin activity (%), International ratio (INR), and serum creatinine), platelet count, presence and degree of ascites, and encephalopathy assessed based on Child-Pugh's criteria.<sup>13</sup>

Patients with mentioned criteria were excluded from the study: those on diuretic or vasoactive treatment, those with previous gastrointestinal bleeding, hepatorenal syndrome during the past 3 month, hepatocellular carcinoma, any history of thrombosis or splenectomy due to any reason, thrombocytosis (platelet count >450000 N/mm<sup>3</sup>), current alcohol intake, previous surgery for portal hypertension or trans-jugular intra-hepatic portosystemic stent shunt placement, and clear signs of portal hypertension (ascites or hepatic encephalopathy).

All patients underwent color Doppler ultrasonic examination after endoscopy by a radiologist blinded to the results of endoscopy. They were evaluated for the presence and grade of EV, and portal hypertension evidences. In the presence of EV, its size was graded as 0-III using the Paquet's grading system.<sup>13</sup> Then patients were classified either as having mod-

erate to severe EVs (grades II-III; Group B) or having mild or no varices (grades 0 or I; Group A). All patients were kept fasting for at least 6hrs prior to the ultrasonography. As well, the main Doppler factors were always taken by the same equipment (with a 3.5-5 MHz curve - array transducer, G-50 Siemens) and by the same operator: i) Portal vein flow velocity as time average maximal velocity in cm/s and portal vein diameter; ii) hepatic artery resistance index (RI) measured in the intrahepatic main branches [ $RI = (systolic\ velocity - end\ diastolic\ velocity) / systolic\ velocity$ ]; iii) splenic artery RI measured intra-parenchymally near to hilum; iv) spleen size (length of its longest axis); and v) presence of portal-systemic collaterals.

The following indices were calculated: i) The liver vascular index as the ratio of portal venous velocity to hepatic arterial resistance index; ii) congestion index (CI) of the portal vein with dividing portal vein cross-sectional area by portal blood velocity; and iii) portal hypertensive index as (hepatic artery  $RI \times 0.69$ ) \* (splenic artery  $RI \times 0.87$ ) / portal vein mean velocity.

Data were analyzed with SPSS for windows version 13. Descriptive statistics including means, standard deviations, and frequencies were computed. The student's t-test was used to compare means of variables. Values were considered significant if  $P < 0.05$  (95% CI). The value of the prediction rule were estimated for indices by means of a receiver operating characteristic (ROC) curve and the area under the curve (AUC) was reported for independent predictors.

## Results

From March 2006 to May 2008, fifty consecutive cirrhotic patients (41 men, 9 women) referring to the gastroenterology clinic of Al-Zahra hospital, Isfahan, were enrolled in this study. Patients' demographic and clinical characteristics are shown in Table 1.

Mean age ( $\pm SD$ ) of these patients was 52.1 (16.2) years (range: 18-83 years). As well, the mean duration of their disease was 33.6 ( $\pm 32.1$ ) months (range: 1-144 months). The diagnosis of cirrhosis had been brought up for these patients using laboratory or clinical examinations or based on liver biopsy. Among the studied probable etiologies of cirrhosis (HBV, HCV, auto-immune hepatitis, HBC/HCV, probably alcohol, and idiopathic causes), HBV and idiopathic causes were most frequent in these patients (each one, 38%). Table 2 shows the frequency percents of studied etiologies. All the studied patients underwent upper GI endoscopy. Based on our endoscopic findings, moderate to severe EV was found in 31 patients

(62%) (Group B: 16 (32%) were in class II, and 15 (30%) were in class III) and 19 patients (38%) had mild (6 patients; 12%) or no (13 patients; 26%) EV (Group A). Based on the endoscopic findings and grade II was the most frequent one among our studied patients. The severity grade frequencies are shown in Table 3. Using t-test, the means of quantitative variables (age, platelet count, serum albumin, total serum bilirubin, SGOT, SGPT, INR, Spleen diameter, Portal vein diameter, Portal vein cross section area, Splenic artery RI, hepatic artery RI, mean portal vein velocity, congestive index, Portal hypertension index, liver vascular index, and platelet count (PC)/spleen diameter (SD) ratio) were compared between groups A and B. It's shown that the means of platelet count and the laboratory amounts of total serum bilirubin, SGOT, and SGPT in group B (patients with moderate to severe EV) were meaningfully more than patients in group A (with mild or no EV) ( $P < 0.0001$ ,

0.041, 0.011, and 0.035, respectively). Also, the mean of PC/SD ratio in group B patients was meaningfully lower than its mean in group A ( $P < 0.0001$ ). For other quantitative diameters, no meaningful difference was found between the two mentioned groups ( $P > 0.05$ ).

We used ROC curve to assess the predicting value of Doppler ultrasonic indices (Figure 1) and the area under the curve (AUC) was calculated for each index. Table 4 shows the measurement of AUC for these assessed indices. As we have considered the  $AUC > 0.7$  to be statistically significant, no one of ultrasonic indices were significant predictors for the presence of EV. Spearman regression was also used to relationship between EV grade and the Doppler ultrasonic indices. Based on our findings, portal hypertension had a direct significant relationship with EV severity ( $P = 0.029$ ), but EV grade had no significant relationship with congestion index and liver vascular index ( $P = 0.055$  and  $0.058$ , respectively).

**Table 1. Description of variables in two studied groups.**

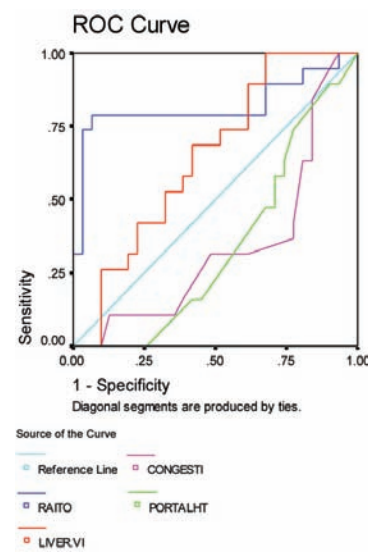
P-value	Group patients A: without EV (Mean $\pm$ SD)	Group patients B: with EV (Mean $\pm$ SD)	Variable
-	19	31	Number of patients
>0.05	52.3(15.9)	52.10 (15.7)	Age(yrs.)
<0.05	126000(49426)	72839(31247)	Platelet count(mm <sup>3</sup> )
>0.05	2.8 (0.76)	2.6(0.74)	Serum Albumin(g/dL)
<0.05	3.8(3.1)	7.4(7.7)	Total bilirubin(mg/dL)
<0.05	70(29.3)	130(96.1)	SGOT(IU/dL)
<0.05	51.8(38.2)	75.7(35.8)	SGPT(IU/dL)
>0.05	1.9(0.73)	2.2(1.09)	INR
<0.05	131.3(24.5)	151.3(30.1)	Spleen diameter(mm)
<0.05	1007.8(425.4)	502.1(233.4)	PC / SD

**Table 2. The frequency of studied etiologies for cirrhosis.**

	Number	%
Auto immune hepatitis	2	4
Unknown	19	38
HBV	19	38
HCV	7	14
HBV/HCV	1	2
Probably alcohol	2	4
Total	50	100

**Table 3. The severity grades frequencies of EVs.**

Grade	Number	%
0	13	26
I	6	12
II	16	32
III	15	30
Total	50	100



**Figure 1. ROC curves for ratio, congestive index, portal Hypertensive index, and Liver vascular index.**

## Discussion

Variceal gastrointestinal bleeding is one of the most common life-threatening complications of portal hypertension with significant morbidity and mortality. Variceal size is identified to be one of the most important factors responsible for first variceal hemorrhage.<sup>21</sup> 10-20% of small varices progress in size during one year<sup>22</sup> which is close to 20-30% risk of bleeding in first 2-year after first detection.<sup>23</sup> It seems that recognizing patients with elevated risk of bleeding for on time interventions will reduce morbidity and financial burden in initial diagnosis or periodic intervals thereafter.

The number of patients undergoing screening for the presence of EV is likely going to increase in the near future as a result of the growing number of patients with chronic liver disease.<sup>24,25</sup> Consensus based guidelines recommend endoscopic screening of all cirrhotic patients for the presence of varices at the time of diagnosis.<sup>26</sup> Relatively low risk of bleeding in compensated cirrhotic patients and a need to avoid invasive and avoidable procedures, suggest performing an upper gastrointestinal endoscopy only on those patients with clinical evidence of portal hypertension.<sup>27</sup> Therefore, there is a particular need for non-invasive predictors of the presence of EV as they might help relieve medical, social, and economic costs. Meanwhile some recent studies addressed newly investigated method, capsule endoscopy, for screening of these patients that can be an acceptable alternative in some conditions but cannot be suggested to replace UGIEs.<sup>28</sup>

We studied 50 of consecutive newly diagnosed cirrhotic patients. The mean age of studied patients was 52.1 ( $\pm 16.2$ ) and EV was present in 62% of them, which are nearly similar to some other same studies<sup>12,13</sup> Based on the statistical findings of our study, no one of sonographic measured characters (spleen size, portal vein diameter and cross section area, resistance of hepatic and splenic arteries, Portal vein flow velocity, congestive index, portal Hypertensive index, and Liver vascular index) had acceptable predictive value for the presence of EV. As well, only the portal Hypertensive index had a significant relationship with the severity of EV and can be used in advanced assessment the patients with well proved varices.

Some other studies have reported the same results as ours. Feng-Hua L et al. have reported that Doppler ultrasonography had no value in the identification of patients with cirrhosis at risk of variceal bleeding.<sup>29</sup> Also, Jeon SW et al. found that Doppler measurement was not helpful in distinguishing the presence of

**Table 4. The amounts of AUC for assessed doppler ultrasonographic indices.**

ROC curve of variables	Area under the curve	Lower	Upper	P
PC/SD	0/82	0/673	0/967	<0/0001
Congestive index	0/34	0/182	0/497	0/059
Portal hypertension index	0/34	0/191	0/489	0/06
Liver vascular index	0/647	0/495	0/798	0/084

varices. However, clinical tests including biochemistry and ultrasonography would be useful in selecting eligible patients for screening endoscopy.<sup>30</sup>

However, many other studies have reported different findings, comparing with our results. Dib et al. have found that the presence of EV is related to the all hepatic and splenic hemodynamic parameters in which, the most accuracy was for splenic arterial resistance and portal Hypertensive index.<sup>13</sup> Also, Testa *et al.* found a significant relationship between the congestive index and the presence of EV.<sup>14</sup>

Schepis F et al. have reported that compensated cirrhotic patients should be screened by upper gastrointestinal endoscopy when prothrombin activity less than 70%, platelet count less than  $100 \times 10^9/L$ , and ultrasonographic portal vein diameter greater than 13 mm are observed, whereas those without any of these predictors should not undergo endoscopy. They also concluded that the contribution provided by portal Doppler ultrasonographic parameters does not appear of practical utility.<sup>31</sup> As well, Sarwar S *et al.* shown that patients with portal vein diameter >11 mm are more likely to have high grade varices.<sup>32</sup>

Prihatini J *et al.* showed that platelet count, portal vein diameter and anteroposterior splenic measurement can be used as non invasive parameters to detect esophageal varices in cirrhotic patients.<sup>33</sup>

Tarzamni MK et al. have suggested two independent situations for beginning endoscopic evaluation of compensated cirrhotic patients: Portal hypertensive index >2.08 and spleen size >15.05 cm. These factors may help identifying patients with a low probability of LEV who may not need upper gastrointestinal endoscopy.<sup>34</sup> Also, Chen-Hua L et al. found that splenoportal index (SPI) can serve as a useful noninvasive index to predict the presence or absence of esophageal varices.<sup>35</sup>

In summary, our data indicate that using Doppler sonographic evaluations does not allow predicting the presence of LEV with a fairly high accuracy. However, values for the non-invasive indicators from this study and comparables need to be validated in more prospective studies with greater sample sizes and better sonographic equipments.

## Appendix

Authors based on present data suggest to use the Doppler assessment as an predictor of severity of varices, especially portal hypertension index. But as primary screening it seems to need more complementary laboratory indices like PC/SD diameter not to miss any probable patient with varices. We recommend to enroll more studies on the the relation of other Doppler indices with severity of varices rather than primery screening.

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