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RAPID COMMUNICATION

Portal hemodynamics as predictors of high risk esophageal varices in cirrhotic patients

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Abstract

AIM: To evaluate portal hypertension parameters in liver cirrhosis patients with and without esophageal varices (EV).

METHODS: A cohort of patients with biopsy confirmed liver cirrhosis was investigated endoscopically and with color Doppler ultrasonography as a possible non-invasive predictive tool. The relationship between portal hemodynamics and the presence and size of EV was evaluated using uni- and multivariate approaches.

RESULTS: Eighty five consecutive cirrhotic patients (43 men and 42 women) were enrolled. Mean age (± SD) was 47.5 (± 15.9). Portal vein diameter (13.88 ± 2.42 *vs* 12.00 ± 1.69, $P < 0.0005$) and liver vascular index (8.31 ± 2.72 *vs* 17.8 ± 6.28, $P < 0.0005$) were found to be significantly higher in patients with EV irrespective of size and in patients with large varices (14.54 ± 1.48 *vs* 13.24 ± 2.55, $P < 0.05$ and 6.45 ± 2.78 *vs* 10.96 ± 5.05, $P < 0.0005$, respectively), while portal vein flow velocity (13.25 ± 3.66 *vs* 20.25 ± 5.05, $P < 0.0005$), congestion index (CI) (0.11 ± 0.03 *vs* 0.06 ± 0.03, $P < 0.0005$), portal hypertensive index (2.62 ± 0.79 *vs* 1.33 ± 0.53, $P < 0.0005$), and hepatic (0.73 ± 0.07 *vs* 0.66 ± 0.07, $P < 0.001$) and splenic artery resistance index (RI) (0.73 ± 0.06 *vs* 0.62 ± 0.08, $P < 0.0005$) were significantly lower. A logistic regression model confirmed spleen size ($P = 0.002$, AUC 0.72) and portal hypertensive index ($P = 0.040$, AUC 0.79) as independent predictors for the occurrence of large esophageal varices (LEV).

CONCLUSION: Our data suggest 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.

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Key words: Liver cirrhosis; Doppler ultrasound; Portal hemodynamics; Esophageal varices; Prediction

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INTRODUCTION

The most common clinical manifestations of portal hypertension in patients with liver cirrhosis are esophageal varices (EV). Bleeding EV are of the most apprehensive complications of portal hypertension contributing to the estimated 32000 deaths annually attributed to cirrhosis[1]. Reducing morbidity and mortality of EV remains a challenge for physicians managing patients with chronic liver disease.

The incidence of EV in patients with cirrhosis ranges from 35% to 80%. Approximately one third of the patients with EV experience variceal bleeding, which in up to 70% of the survivors is followed by repeated bleeding episodes[2]. Esophageal variceal bleeding might be a deadly complication in liver cirrhosis patients with portal hypertension[3,4]. A screening is indicated in patients with newly diagnosed cirrhosis. Medical treatment must be considered as soon as varices are detected to prevent a first bleeding[5].

It has been shown that the risk of EV bleeding is related to its size[6]. Large esophageal varices (LEV) are at a greater risk, which is possibly due to a higher variceal wall tension[7]. Availability of non-invasive methods for detection of LEV may help limit the number of endoscopic procedures.

The estimation of blood flow volume with Doppler sonography is non-invasive and allows physiologic measurements that were impossible to obtain in the past. It was widely used to explore the relationship between EV hemodynamics associated with portal hypertension and liver cirrhosis[8,9]. Main characteristics of portal hypertension like a decrease in portal flow velocity or an increase in portal vein diameter are detectable by this means[10,11]. However, no consistent alternative has been reported to replace endoscopic assessment of such patients through time yet. In this study, we investigated the hemodynamic features of the portal vein in two groups of patients with liver cirrhosis, namely those with and those without EV, as well as considering large varices with an advanced risk of bleeding.

MATERIALS AND METHODS

Consecutive newly diagnosed cirrhotic patients who were visited at our institute participated in a prospective study from May 2006 to August 2007 prior to treatment. The diagnosis of cirrhosis was based on a liver biopsy evaluation. Patients on diuretic or vasoactive treatment, with previous gastrointestinal bleeding, hepatorenal syndrome during the past 3 mo, evidence of portal vein thrombosis on ultrasonography, and patients with clear signs of portal hypertension (ascites, porto-systemic shunts or hepatic encephalopathy) were excluded.

All patients underwent endoscopy after color Doppler-ultrasonic examination by the same gastroenterologist blinded to the results of duplex Doppler. They were evaluated for the presence and grade of EV, the presence of gastric varices, and portal hypertensive gastropathy (PHG). In the presence of EV, size was graded as Ⅰ-Ⅳ using the Paquet grading system[12]. Moreover, patients were classified either as having LEV (grade Ⅲ-Ⅳ) or not (no varices or grade Ⅰ-Ⅱ).

All patients were kept fasting overnight prior to the procedure at our institution. They were examined in the supine position during quiet respiration. The following main Doppler factors were always taken by the same equipment (with a 3.5- MHz linear - array transducer, EUB-525 Hitachi) and by the same operator (k = 0.80): (1) Portal vein flow velocity as time average maximal velocity in cm/s and portal vein diameter[13]; (2) hepatic artery resistance index (RI) measured in the intrahepatic main branches[14] [RI = (systolic velocity - end diastolic velocity)/systolic velocity]; (3) splenic artery RI measured intraparenchymally near to hilum[15]; (4) spleen size (length of its longest axis); and (5) presence of portal-systemic collaterals.

The following indices were calculated: (1) The liver vascular index as the ratio of portal venous velocity to hepatic arterial pulsatility index; (2) congestion index (CI) of the portal vein with dividing portal vein cross-sectional area by portal blood velocity[16]; and (3) portal hypertensive index as (hepatic artery RI*0.69)*(splenic artery R*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 chi square test was used to compare differences, and student's *t* test was used to compare means of variables. Values were considered significant if $P < 0.05$ (95% CI). A logistic regression equation was developed to predict presence and grade of EV. The sensitivity and specificity of the prediction rule were estimated by means of a receiver operating characteristic (ROC) curve and area under the curve (AUC) was reported for independent predictors.

Table 1 Baseline characteristics of 85 cirrhotic patients [as *n* (%) or mean ± SD]

Gender	
Male	43 (50.6)
Female	42 (49.4)
Etiology	
Hepatitis B virus (HBV)	40 (47.0)
Hepatitis C virus (HCV)	12 (14.1)
Cryptogenic	14 (16.5)
Autoimmune hepatitis (AIH)	17 (20.0)
Alcohol	2 (2.4)
Wilson's disease	1 (1.2)
Size of esophageal varices	
None	16 (18.8)
Small (grade I-II)	50 (58.8)
Large (grade III-IV)	19 (22.3)
Size	7.9 (± 3.4)
Gastric varices	11 (12.9)
Portal hypertrophic gastropathy	75 (88.2)
Portal vein diameter (mm)	13.5 (± 2.4)
Splenic axis (cm)	15.7 (± 3.1)
Portal vein flow (cm/s)	14.6 (± 4.8)
Splenic artery resistance	0.7 (± 0.1)
Hepatic artery resistance	0.7 (± 0.1)

RESULTS

Eighty five consecutive cirrhotic patients (43 men, 42 women) were enrolled in the study. Mean age (± SD) of the study population was 47.5 (± 15.9) years. Table 1 shows the patients' baseline characteristics. Hepatitis B virus (HBV) infection was the only cause of cirrhosis in most of our patients.

Thirteen patients had EV grade 1, 37 grade 2, and 19 grade 3. Gastric varices were detected in 11 patients (ten type 1 and one type 2).

Univariate analysis showed that most of the echo-Doppler parameters were related to presence of EV (Table 2). Portal vein flow velocity and liver vascular index was significantly higher in patients with EV while they had lower portal vein diameter, CI, portal hypertensive index, and hepatic and splenic artery RI. Presence of LEV was related to all of the echo-Doppler parameters described in Table 3.

Portal hypertensive index ($P = 0.002$) and congestive index ($P = 0.002$) were significantly higher, and portal vein flow velocity ($P < 0.0005$) and liver vascular index ($P \leqslant 0.0005$) were significantly lower in patients with PHG. Liver vascular index was independently correlated with PHG ($P = 0.018$). Portal PHG was present in 94.2% of the patients with EV ($P = 0.002$) and in all of the patients with gastric varices.

A logistic regression model showed that the parameters were not a good predictor of the presence of esophageal or gastric varices. However, spleen size and portal hyper-

Table 2 mean ± SD of the primary and derivative echo-Doppler factors in study population according to presence of esophageal varices in any size

	With EV	Without EV	*P* value	AUC
Portal vein flow velocity (cm/s)	13.25 ± 3.66	20.25 ± 5.05	< 0.0005	0.113
Portal vein diameter (mm)	13.88 ± 2.42	12.00 ± 1.69	0.004	0.242
Hepatic artery resistance index	0.73 ± 0.07	0.66 ± 0.07	0.001	0.210
Splenic artery resistance index	0.73 ± 0.06	0.62 ± 0.08	< 0.0005	0.168
Spleen size (cm)	15.98 ± 3.01	14.76 ± 3.66	0.166	0.431
Liver vascular index	8.31 ± 2.72	17.08 ± 6.28	< 0.0005	0.114
Congestion index	0.11 ± 0.03	0.06 ± 0.03	< 0.0005	0.128
Portal hypertensive index	2.62 ± 0.79	1.33 ± 0.53	< 0.0005	0.072

EV: Esophageal varices; AUC: Area under the curve.

Table 3 mean ± SD of the primary and derivative echo-Doppler factors according to presence of large esophageal varices

	With LEV	Without LEV	*P* value	AUC
Portal vein flow velocity (cm/s)	12.13 ± 2.59	15.26 ± 5.06	0.001	0.715
Portal vein diameter (mm)	14.54 ± 1.48	13.24 ± 2.55	0.037	0.748
Hepatic artery resistance index	0.80 ± 0.06	0.70 ± 0.06	0.003	0.820
Splenic artery resistance index	0.76 ± 0.11	0.69 ± 0.06	< 0.0005	0.656
Spleen size (cm)	17.62 ± 3.05	15.21 ± 2.99	0.003	0.724
Liver vascular index	6.48 ± 2.78	10.96 ± 5.05	< 0.0005	0.817
Congestion index	0.14 ± 0.04	0.09 ± 0.03	< 0.0005	0.797
Portal hypertensive index	3.18 ± 0.90	2.14 ± 0.77	< 0.0005	0.791

LEV: Large esophageal varices; AUC: Area under the curve.

tensive index were reported as predictors of LEV as presented in Table 4. We examined threshold values for these independent predictors of LEV for achieving a sensitivity > 75%. Portal hypertensive index > 2.08 and spleen size > 15.05 cm reached a sensitivity of 79% for detecting LEV.

Table 4 Logistic regression model to predict the presence of large esophageal varices in newly diagnosed patients with compensated cirrhosis

	P value	Odds ratio	95% CI
Congestive index	0.252	0	-
Portal hypertensive index	0.040	4.83	1.08-21.65
Liver vascular index	0.151	0.72	-
Spleen size	0.002	1.77	1.23-2.55

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[17]. 10% to 20% of small varices progress in size during one year[18] which is close to 20% to 30% risk of bleeding in first 2-year after first detection[19]. It seems that recognizing patients with elevated risk of bleeding for on time interventions will reduce morbidity and cost in initial diagnosis or periodic intervals thereafter.

Consensus based guidelines recommend endoscopic screening of all cirrhotic patients for the presence of varices at the time of diagnosis[20]. Relatively low risk of bleeding in compensated cirrhotic patients and a need to avoid invasive and avoidable procedures, suggests performing an upper gastrointestinal endoscopy only on those patients with clinical evidence of portal hypertension[21].

Even though, the available data are insufficient to determine a reliable non-invasive predictive tool to categorize cirrhotic patients along with significant risk for bleeding. Researchers have designed studies based on clinical, biochemical, and radiographic measurements as to when one should begin endoscopic screening for the presence of EV with cirrhosis. Such attempts have been made to identify non-invasive procedures for either reducing or eliminating the need for screening endoscopy. Researchers support non-invasive methods (duplex Doppler sonography) in measurement of functional hepatic flow in cirrhotic patients, which can estimate hepatic reserve function[22].

Our study, based on information achieved from newly diagnosed compensated liver cirrhosis patients demonstrated a correlation of portal hemodynamics with the presence of LE and with a higher diagnostic accuracy with LEV on univariate analysis. However, on multivariate analysis, only increased spleen size and portal hypertensive index were found to have an independent predictive value which has been the most consistently identified predictors in previous studies. Our data suggests two independent situations for beginning endoscopic evaluation of compensated cirrhotic patients: Portal hypertensive index > 2.08 and spleen size > 15.05 cm; restraining the need for upper gastrointestinal endoscopy of compensated cirrhosis.

It may be explained according to the issue that palpable spleen as well as LEV may both be related to the presence of a higher portal pressure. Different factors found to be important for this purpose included splenomegaly[23-28], thrombocytopenia[23-30], ascites[25,27], hepatic encephalopathy[25], serum albumin concentration[30], serum bilirubin levels[30], and Child-Pugh score[27,28]. Thus, the results of our study are consistent with those of the previously published data.

Echo-Doppler parameters like splenic artery RI and portal hypertensive index have been reported to have a specificity > 70% (for most thresholds) when comparing portal hypertensive patients with CLD patients without clinically relevant portal hypertension[8].

Esophagogastric varices exactly reflect the presence of portal hypertension. But the correlation between esophagogastric varices and PHG is obscure[31]. Our study revealed a correlation between EV and the presence of gastropathy, and all of the patients with LEV had gastropathy.

Our study group represented a selected group of patients with liver cirrhosis attending a tertiary care center, but criteria for excluded patients (clear signs of portal hypertension) and preferring patients without history of GI bleeding achieved a better sample. Results would be best applied in patients attending large hospitals and further studies will be necessary regarding this aspect. Such studies may be particularly indicated because of

differences in the etiology of liver disease in dissimilar populations. The most common etiologies of cirrhosis in our population are either cryptogenic or HBV infection[32].

Our data indicate that using non-invasive tools for estimating spleen size and portal hypertensive index allows predicting the presence of LEV with a fairly high accuracy. Values for the non-invasive indicators from this study and comparables need to be validated in a prospective study. Selecting patients for an upper GI endoscopy may be cost effective and, on the other hand, will define patients who need a critical management.

COMMENTS

Background

Bleeding esophageal varices (EV) are of the most apprehensive complications of portal hypertension in patients with liver cirrhosis. EV bleeding is a potentially deadly complication in such patients and is considered as an indication for screening in patients with newly diagnosed cirrhosis.

Research frontiers

Availability of non-invasive methods may help limit the number of endoscopic procedures performed for detection of large esophageal varices (LEV) which hold the higher risk for bleeding.

Related publications

Researchers have mentioned relations between portal hemodynamic situation and risk of EV or bleeding of them but available data are still insufficient to determine a reliable non-invasive predictive tool to categorize cirrhotic patients along with significant risk for bleeding.

Innovations and breakthroughs

This study evaluates newly diagnosed patients with no complications who may benefit from non-invasive procedures. Etiology of liver cirrhosis in our study population is different from Western community.

Applications

Using non-invasive tools for estimating spleen size and portal hypertensive index makes it possible to predict the presence of LEV. These values should ultimately be validated in a prospective study before being used to determine which patients should undergo esophageal variceal screening endoscopy.

Terminology

Size of the spleen and portal hypertensive index are measured by ultrasonography. Portal hypertensive index in details is (Hepatic artery RI*0.69)*(splenic artery RI*0.87)/portal vein mean velocity.

Peer review

It is a nice study to evaluate and compare the differences in the parameters of portal hypertension in liver cirrhosis patients with and without esophageal varices.

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