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NON-INVASIVE PREDICTORS OF PORTAL HYPERTENSION IN PATIENTS WITH HEPATITIS C VIRUS RELATED HEPATOCELLULAR CARCINOMA

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Abstract
The reference standard for portal venous pressure measurement which is clinically important for estimating the feasibility of resection of hepatocellular carcinoma is the hepatic venous pressure gradient, which is invasive and expensive. The present study evaluated the non-invasive parameters for assessment of portal hypertension in Child A patients with hepatocellular carcinoma on top of hepatitis C virus.

A total of 112 patients were subjected to clinical assessment, biochemical assay, ultrasonographic Doppler study, triphasic spiral abdominal computed tomography, upper gastrointestinal endoscopy and hepatic venous pressure gradient measurement. According to hepatic venous pressure gradient measurement, they were classified into groups: GI: 58 patients with hepatic venous pressure gradient <10 mmHg and GII: 54 patients with hepatic venous pressure gradient ≥ 10 mmHg. Significant variables in univariate analysis were included in a multivariate analysis to establish a model for prediction of clinically significant portal hypertension.

Results showed that portal vein diameter ≥ 1.3 cm, mono or biphasic pattern of flow in hepatic veins and Giannini index ≤ 909 were independent risk factors for the clinically significant portal hypertension as indicated by HVPG ≥ 10 mmHg. A model with highest likelihood ratio and good fitness was created. This prediction model was displayed by the receiver operating characteristic curve and under the curve area was 0.969 (0.938-1).

Keywords Hepatocellular carcinoma, Hepatic venous pressure gradient, Portal vein diameter, Hepatic vein, Giannini index

Introduction

In the setting of cirrhosis, measurement of portal venous (PV) pressure is clinically important when diagnosing portal hypertension, estimating the likelihood of variceal bleeding, monitoring the progress of therapy (De Franchis *et al,* 2008) and also assesses feasibility of resection in patients with hepatocellular carcinoma (HCC) (Parikh, 2009). Normal bilirubin concentration and hepatic vein pressure gradient (HVPG) of less than 10 mmHg in Child A cirrhotic patients are the best predictors of excellent outcome after resection and are associated with almost no risk of postoperative liver failure with 70% 5-year survival (Llovet *et al*, 2008). The reference standard for measurement of portal venous pressure is HVPG calculated by subtracting the free hepatic venous pressure from the wedged hepatic venous pressure. Unfortunately, calculation of HVPG is invasive and expensive, and it cannot be used to monitor therapy. An accurate noninvasive technique that could be used to measure portal venous pressure would represent a major advance in the diagnosis and management of portal hypertension (Parikh, 2009). Several clinical, biochemical, and imaging parameters alone or together have good predictive power for non-invasive assessment of portal hypertension. Some parameters have been found to have a high specificity and sensitivity for the diagnosis of cirrhotic portal hypertension with ultrasound colour duplex Doppler examination such as coarse shrunken liver, dilated portal vein (diameter > 13 mm), size of spleen, splenic vein (SV) diameter and ascites (Cottone *et al*, 1986), lack or reduced respiratory variations of splenic and superior mesenteric vein diameter (Bolondi *et al*, 1982), reversal of portal blood flow, reduced portal vein velocity (Zoli *et al*, 1993), portal-systemic collateral circulation (van Leeuwen, 1990), altered hepatic venous Doppler pattern (Baik *et al*, 2006), increased intraparenchymal hepatic and splenic artery impedance (Sacerdoti *et al*, 1991; Bolognesi *et al*, 2001), increased intraparenchymal renal artery impedance (Berzigotti *et al*, 2006), increased congestion index of portal vein (Moriyasu *et al*, 1986) and reduced mesenteric artery impedance (Taourel *et al*, 1998).

The present study evaluated clinical, biochemical and ultrasonographic Doppler parameters with good predictive power for non-invasive assessment of portal hypertension in Child A patients with HCC on top of HCV related chronic liver disease so that to be excluded from hepatic resection list.

Patients and Methods

The present study was cross-sectional comparative conducted on 112 patients with HCC admitted from November 2010 to August 2013. The study was approved by the medical ethics committee of Ain Shams University and conducted in accordance with the principles of the declaration of Helsinki. All patients provided written informed consent before enrollment. Inclusion criteria were patients with HCV related chronic liver disease, Child class (A) with HCC which was diagnosed according to the following suggested alghorism shown in fig.1 for the diagnostic strategy after detection of hepatic nodule by ultrasound (Bruix and Sherman, 2005); absence of portal, splenic, hepatic vein thrombosis, any vascular invasions or arterio-venous fistula; absence of previously sclerosis or band ligation of oesophageal varices, transjugular intrahepatic portosystemic stent shunt, or surgery for portal hypertension; absence of drug intake for primary prophylaxis of variceal bleeding or previously any intervention for HCC.

Study Design and procedures

All patients were subjected to complete history taking, thorough clinical examination, laboratory investigations including complete blood count, liver profile, renal profile, hepatitis C virus antibody using third generation ELISA test and serum alpha-fetoprotein. Abdominal color Doppler ultrasonographic study by an ultrasound machine (Logic 9, General Electric, medical systems, Milwaukee, USA) was used, after 6 hours fasting, to assess the liver (size and echogenicity), portal vein (patency, diameter, portal vein cross sectional area, mean portal vein flow velocity and direction of flow), hepatic venous Doppler pattern, hepatic artery resistance index, spleen size, splenic vein (patency, diameter, splenic vein cross sectional area, mean splenic vein flow velocity), splenic artery resistance index, intraparenchymal renal artery resistive index (RARI), status of ascites and portosystemic collaterals. The portal vein cross sectional area (PV CSA) (cm^2) was obtained assuming portal vein to be circular in cross section and calculated by the computer software of the machine up to 0.99 cm^2 in normal subjects (Moriyasu *et al*, 1986; Pozniak, 2002). The average mean portal vein flow velocity (mean PVV) (cm/sec) is above 19 cm/sec in normal subjects (Ozaki *et al*, 1988). Direction of flow was assessed so that if the flow is towards the transducer, it displays red color (hepatopetal), but if the flow is away from the transducer, it displays blue color (hepatofugal). In cases with both red and blue colors, the flow is bi-directional. The splenic vein cross sectional area (SV CSA) (cm^2) and mean splenic vein flow velocity (mean SVV) (cm/sec) were calculated in the same way described with the portal vein. The normal SV CSA is up to 0.5 cm^2 and the average mean SVV is 19.9 ± 4.6 cm/sec in normal subjects (El Zeiny *et al*, 2002). Hepatic artery resistance index (HARI) was measured in the intrahepatic main branches. The resistance index (RI) was calculated over one cardiac cycle from the formula: RI = (systolic velocity-end diastolic velocity)/ systolic velocity (this was calculated by machine software). Average value was 0.68 in normal one (Schneider *et al*, 1999). Splenic artery resistance index (SARI) was measured intra-parenchymally, near to the hilum. It was calculated like HARI, cutoff value is 0.60 in normal subjects (Sacerdoti *et al*, 1991). The reported values of the Doppler parameters were obtained by taking the average value of 3 consecutive measurements. Also the following indices were calculated; congestion index (CI) (cm/sec-1) which was calculated for portal and splenic veins as: CI = CSA/mean velocity, The average PV CI in normal subjects is up to 0.07 cm/sec-1 and the average SV CI is up to 0.04 cm/sec-1 (Pozniak, 2002; El Zeiny *et al*, 2002). Modified liver vascular index (MLVI) (cm/sec) was calculated as: portal flow velocity/ hepatic artery RI (Piscaglia *et al*, 2001). Portal hypertension index (PH index) (m/sec-1) was calculated as: [(hepatic artery RI × 0.69) × (splenic artery RI × 0.87)]/ portal vein mean velocity (Piscaglia *et al*, 2001). Porto-systemic collaterals e.g. left gastric vein, paraumbilical vein, porta hepatis collaterals, lienorenal collaterals, splenic hilar collaterals and gastrorenal collaterals were also examined. Hepatic venous Doppler pattern was assessed either monophasic, biphasic or diphasic. Platelet count/spleen diameter ratio was calculated in millimeters by Giannini index (Giannini *et al*, 2003**)**. Upper gastrointestinal (GIT) endoscopy Pentax EG-3440 videoscope system was used to evaluate the presence and degree of varices in addition to any relevant upper GIT lesions. Triphasic spiral abdominal computed tomography (CT) was done to diagnose HCC by typical vascular pattern and to assess tumor site, size, number and extension. HVPG was measured with the patients under local anesthesia, a venous introducer was placed in the right internal jugular vein and a 5 French catheter with cobra head configuration was advanced under fluoroscopic control into the main right hepatic vein. Using an invasive monitor, pressure was measured while tip of catheter was floating in the middle of the hepatic vein (free hepatic venous pressure (FHVP). The catheter is then pushed down in the hepatic vein until it cannot be advanced further, which results in a complete obstruction of flow (position of catheter was confirmed by using contrast material); the pressure recorded in the occluded position (using invasive monitor) is the wedged hepatic venous pressure (WHVP). HVPG was calculated by subtracting the FHVP from the WHVP. The HVPG is the difference between the portal vein and the inferior vena cava pressures (IVCP) and represents the real perfusion pressure within the portal and hepatic circulations. Normal HVPG is about 1-5 mmHg. When HVPG increases above 10-12 mmHg, a number of life-threatening complications can occur (Parikh, 2009).

Statistical analysis: Data were analyzed using SPSS for Windows (version 19.0). Continuous variables were expressed in term of mean and standard deviation (except for alpha-fetoprotein which was expressed in term of median and inter-quartile range) and ordinal and nominal categorical data were described as number and percentages (frequency). Chi-square test with Yates correction and Fisher-Exact were used to test association between two categorical variables. Student-t-test was used to test means' differences between groups (except for alpha-fetoprotein where Mann Whitney test was used). Variables were significant at $P<0.05$. Logistic regression analysis was performed to identify variables independently associated with presence of clinically significant portal hypertension and established model for prediction significant portal hypertension in patients. As all significant variables in univariate analysis could not be included in the same regression model, different models were generated. The best one was judged by likelihood ratio, significance of introduced predictors, odds ratio and confidence interval together with fitness and productivity of the model.

Results

As to HVPG measurement, patients were classified into two groups: GI included 58 patients (51.8%) with HVPG less than 10 mmHg. Mean HVPG was 5.5+/-1.8 mmHg. GII included 54 patients (48.2%) with HVPG equal to or more than 10 mmHg. Mean HVPG was 15.2 +/- 2.3 mmHg. Demographic profile and laboratory parameters were similar in both groups except a lower statistical significant difference in GII in comparison to GI regarding hemoglobin level, white blood cells and platelet counts. Patients in GII had statistically higher values of creatinine and alpha fetoprotein in comparison to GI. All patients had coarse echogenicity of liver with no detectable ascites on abdominal ultrasonography. Most of them had single hepatic focal lesion (HFL) in the right lobe of the liver. Patients in GII had larger spleen, more frequent to have collaterals and their Giannini index was significantly lower than patients in GI. As to upper GIT endoscopy findings, esophageal varices, fundal varices and portal hypertensive gastropathy (PHG) were significantly common in GII than GI (Tab. 1). All patients had patent portal vein with hepatopedal direction of flow and patent splenic vein. Doppler parameters were higher in GII compared to GI with a highly significant difference (Tab. 2).

Significant variables in univariate analysis were included into a binary logistic regression analysis stepwise method. The best predictive model gave the highest likelihood ratio; the relatively high predictivity meanwhile showed a good fitting using Hosmer & Lemshow Goodness of fit test. Portal vein diameter more than or equal to 1.3 cm, mono or biphasic pattern of flow in hepatic veins and Giannini index below or equal to 909 were found to be independent risk factors for presence of clinically significant portal hypertension as indicated by HVPG more than 10 in this study (Tab. 3). The performance of this prediction model is displayed by the receiver operating characteristic (ROC) curve. The area under the curve (AUC) was 0.969 (0.938-1), showed that this model gave a good discrimination between patients with HVPG more than 10 and those with lower HVPG (Fig. 2). A total of 37 patients fulfilled all parameters included in model (Predicted probability = .98260); only one had HVPG less than 10 and 20 had none of model parameters positives (Predicted probability= .00238); all had HPVG less than 10, an example of the general result that if log [P (Y=1)/ P (Y=0)] = $b_0 + b_1 X_1 + .. + b_p X_p$ then "P (Y=1)=exp ($b_0 + b_1 X_1 + .. + b_p X_p$)]" or "P (Y=1) =1/ {1 + esp [- ($b_0 + b_1 X_1 + .. + b_p X_p$)]}" So, P (Predicted probability of High HVPG) = 1/1+exp {-(constant (-6.039) + 4.51(when PV diameter 1.3 or more) + 3.55 (when mono- or biphasic HV Doppler pattern) + 2.01(when PLT/ spleen ratio 909 or less)}

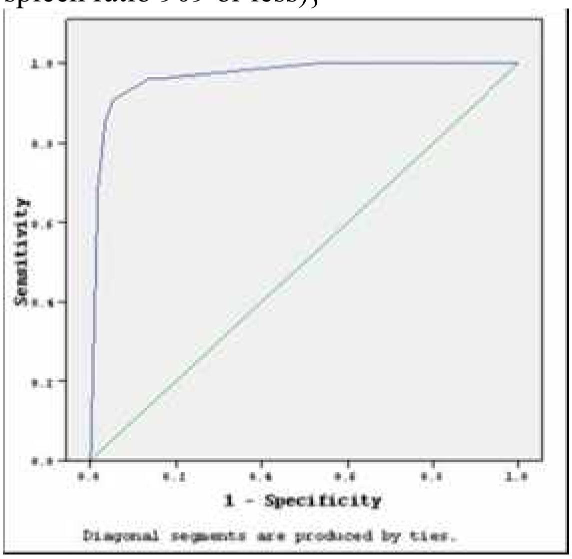

Fig. 1: ROC curve displaying discrimination ability of predictors model for HVPG (AUC 0.969 - 95% CI 0.938-1.0).

ROC receiver operator characteristic, AUC area under curve.

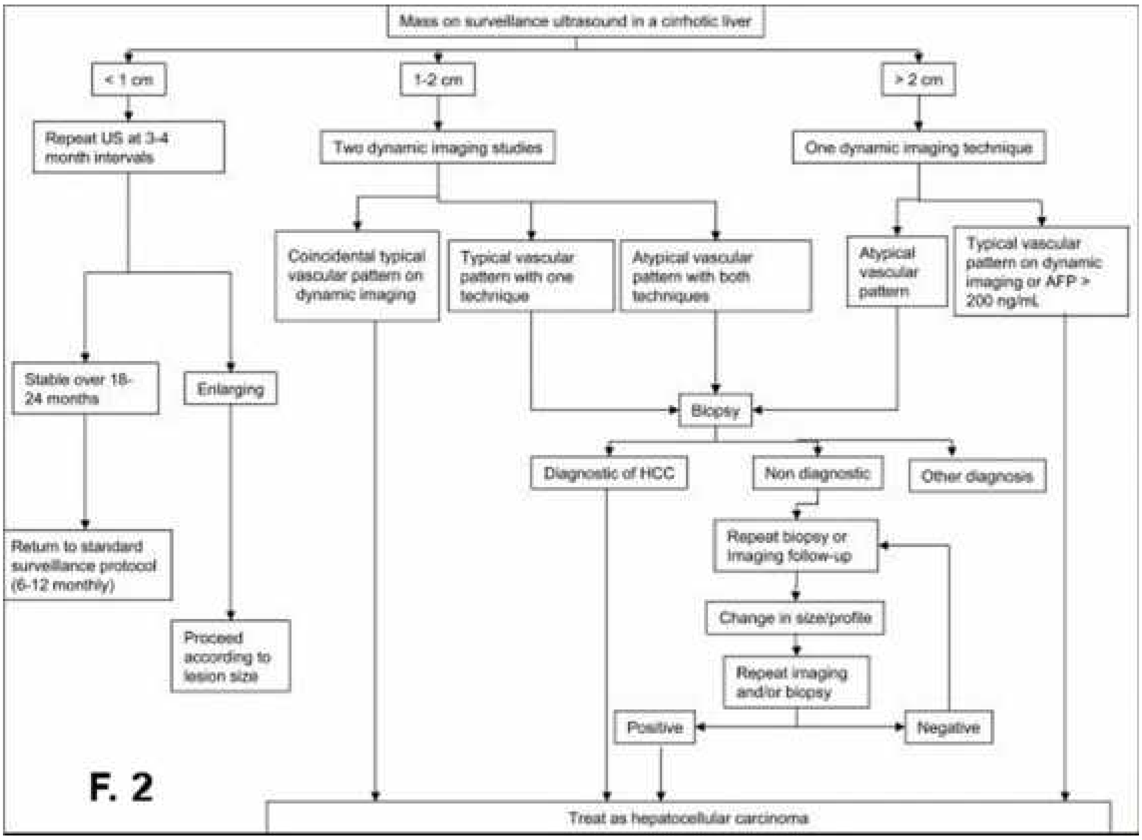

Fig. 2: Algorithm to investigate nodule in ultrasound during screening or surveillance (Bruix and Sherman, 2005).

Table 1: Characteristics of study population

Variable	GI (N=58)	GII (N=54)	*P* value
Age (Years)	55.97 ± 7.284	55.96 ± 5.956	0.998
Sex (Male/Female)	49/9	41/13	0.255
Hemoglobin(gm/dl)	13.410 ± 1.0327	12.902 ± 1.2369	0.020
White blood cells(10^9/L)	5.888 ± 1.9256	4.739 ± 1.4060	<0.001
Platelets(10^9/L)	154.52 ± 46.678	96.09 ± 37.913	<0.001
Alanine transaminase (U/L)	62.24 ± 25.461	55.50 ± 18.137	0.108
Creatinine (mg/dl)	0.856 ± 0.1456	0.999 ± 0.1708	<0.001
Alpha fetoprotein (ng/dl)	44.50 (IQR=14.3-188.58	102 (IQR=30.5-1004.5	0.005
Liver size (shrunken/average/enlarged)	2/40/16	0/45/9	0.086
Collaterals	1	27	<0.001
Splenic diameter (cm)	13.48 ± 1.78	16.63 ± 2.53	<0.001
No. of HFLs (1/2/3)	44/12/2	45/8/1	0.602
Site of HFLs (Right lobe/Left/Both)	44/14/0	46/5/3	0.14
Size of largest HFL (cm)	4.866 ± 1.77	5.159 ± 2.0481	0.420
Oesophageal varices	10 (17.2%)	54 (100%)	<0.001
Fundal varices	0 (0%)	13 (24.1%)	<0.001
PHG	7 (12.1%)	34 (63 %)	<0.001
Giannini index (mm)	1159.82 ± 345.66	611.89 ± 305.04	<0.001

Table 2: Independent factors predicting HVPG

Variables	B[a]	SE[b] of B[a]	P value	OR[c] (95% CI[d])
PV Diameter ≥ 1.3 cm	4.51	0.88	<0.001	90.9 (15.9 - 518.2)
Mono/Biphasic hepatic veins doppler pattern	3.55	1.10	0.001	34.8 (3.9 - 303.9)
Giannini Index ≤ 909	2.01	0.81	0.013	7.5 (1.5 - 36.3)
Constant	6.039	1.345	<0.001	

[a]B=Regression Coefficient, [b]SE=Standard Error, [c]OR=Odds Ratio and [d]CI=Confidence Interval.

Table 3: Comparison between groups regarding Doppler parameters.

Variable		GI (N=58)	G II (N=54)	*P* value
PV diameter (cm)		1.033 ± 0.1559	1.559 ± 0.2469	< 0.001
PV CSA (cm2)		1.124 ± 0.2189	1.997 ± 0.5512	
mean PVV (cm/sec)		21.68 ± 2.848	12.69 ± 2.360	
PV CI (cm/sec-1)		0.06958 ± 0.086437	0.16984 ± 0.078771	
SV diameter (cm)		0.658 ± 0.1003	0.985 ± 0.1951	
SV CSA (cm2)		0.576 ± 0.0927	0.934 ± 0.2529	
mean SVV (cm/sec)		19.22 ± 2.120	12.83 ± 2.309	
SV CI (cm/sec-1)		0.03048 ± 0.007121	0.07704 ± 0.031416	
HARI		0.6409 ± 0.04426	0.7050 ± 0.06737	
SARI		0.6267 ± 0.03827	0.6726 ± 0.04020	
RARI		0.6164 ± 0.04483	0.6757 ± 0.05236	
MLVI (cm/sec)		33.974 ± 5.5116	18.251 ± 4.2253	
PH index (m/sec-1)		0.01138 ± 0.002239	0.02350 ± 0.006442	
Hepatic veins Doppler pattern				
	Monophasic	0 (0%)	14 (25.9%)	
	Biphasic	28 (48.3%)	37 (68.5%)	
	Triphasic	30 (51.7%)	3 (5.6%)	

Discussion

In Egypt, there was a growing incidence of HCC (10-120/100,000), which represents the leading cause of death from all other cancer sites (El-Zayadi *et al*, 2010). Resection and transplantation achieve the best outcomes in well-selected candidates; 5-year survival of 60-80% (Llovet *et al*, 2012). The selection of optimal candidates for liver resection is usually based on the degree of portal hypertension (Llovet *et al*, 2008). The reference standard for measurement of portal venous pressure is the HVPG which is invasive and expensive (Parikh, 2009).

In the present study, both groups were age and sex matched without significant differences between them. Hemoglobin level, white blood cells and platelet counts showed significant lower differences in GII in comparison to GI agreed with others (Sharma *et al*, 2007; Qamar *et al*, 2008), also thrombocytopenia was correlated with clinically significant portal hypertension by HVPG more than 10 (Zaman *et al*, 1999; Berzigotti *et al*, 2013).

In the current study, no significant difference was detected between studied groups regarding alanine transaminase values. Other studies did not elicit association between liver enzymes values and clinically significant portal hypertension detected by presence of esophageal varices (Jeon *et al*, 2006; Sharma *et al*, 2007; Fagundes *et al*, 2008), but, one study established a predictive model for detecting patients with clinically significant portal hypertension using alanine transaminase, albumin and international normalized ratio (Berzigotti *et al*, 2008).

The present patients with clinically significant portal hypertension (CSPH) had statistical high creatinine values than the others (Woitas *et al*, 1997; Rendón Unceta *et al*, 2001) but disagreed by others (Zaman *et al*, 1999; Berzigotti *et al*, 2008; Abuel Makarem *et al*, 2011) which found that portal hypertension in patients with cirrhosis was either compensated or not. Alpha fetoprotein-was significantly higher in CSPH patients that agreed with Ripoll *et al*. (2009), who found that portal hypertension was an independent predictor of HCC development in patients with compensated cirrhosis due to structural abnormalities, fibrogenesis and neoangiogenesis processes. Significant differences were between groups as to presence of collaterals and longest axis diameter of spleen on ultrasound imaging in CSPH patients that agreed with authors (Sarangapani *et al*, 2010; Berzigotti *et al*, 2011; Cherian *et al*, 2011; Esmat *et al*, 2011). Also, no statistical difference was found between groups as to number, extension or size of largest hepatic focal lesion; as patients were selected with child A compensated cirrhosis without vascular invasion or extrahepatic spread. Gastroesophageal varices was commonest in patients with CSPH with highly significant difference that agreed with others (Garcia-Tsao *et al*, 1985; Groszmann *et al*, 1990). Portal hypertensive gastropathy significantly higher in same patients agreed with others (Kim *et al*, 2010; Kumar *et al*, 2010).

In this study, Giannini index was significantly lower in patients with CSPH with high statistical significant difference which is consistent with other studies (Giannini *et al*, 2003; 2006; Sharma *et al*, 2007; Agha *et al*, 2009; Barrera *et al*, 2009; Sarangapani *et al*, 2010; Abu El Makarem *et al*, 2011; Ying *et al*, 2012). This went with other studies (Iwao *et al*, 1997; Plestina *et al*, 2005; Jeon *et al*, 2006; Tarzamni *et al*, 2008; Sarangapani *et al*, 2010; Cherian *et al*, 2011; Hong *et al*, 2011), the present study showed significant statistical differences between groups as to portal vein diameter, portal vein cross sectional area, portal vein mean flow velocity and portal vein congestion index. Others (Zaman *et al*, 1999; Choi *et al*, 2003) found no relation between Doppler parameters and HVPG due to significant variability in portosystemic collateral patterns (Merkel *et al*, 1998). The significant differences were between groups as to splenic vein diameter, splenic vein cross sectional area, splenic vein mean flow velocity and splenic vein congestion index agreed with others (Rodriquez *et al*, 1999; El Zeiny *et al*, 2002; Kayacetin *et al*, 2004), but differed due to lower sample sizes (De Bem *et al*, 2006) or due to liver disease with bleeding varices (Choi *et al*, 2003).

In the present study, HARI, SARI & RARI were highly significantly increased in CSPH patients compared to those without, who agreed with other studies (Piscaglia *et al*, 1997; Colli *et al*, 2001; Berzigotti *et al*, 2006; 20; Vizzutti *et al*, 2007; Zhang *et al*, 2007; Tarzamni *et al*, 2008); nut disagreed with Choi *et al*. (2003). Also, the present PHI were significantly higher in patients with portal hypertension while MLVI was significantly lower which agreed with others (Iwao *et al*, 1997; Amer *et al*, 2001; Piscaglia *et al*, 2001; Haktanir *et al*, 2005; Zhang *et al*, 2007; Tarzamni *et al*, 2008).

In the present study, loss of triphasic hepatic venous waveform was commonest in patients with CSPH, which agreed with two studies (Kim *et al*, 2007; Joseph *et al*, 2011), **but** disagreed with one study (Bhutto *et al*, 2012). Also, as all significant variables in univariate analysis could not be included in same regression model, different models were generated that gave highest likelihood ratio and good fitness. Portal vein diameter more than or equal to 1.3 cm, mono or biphasic pattern of flow in hepatic veins and Giannini index below or equal to 909 (Giannini *et al*, 2003) were independent risk factors for clinically significant portal hypertension by HVPG more than 10 mmHg. Performance of prediction model was displayed by ROC curve. AUC was 0.969 (0.938-1). The model gave a good discrimination between patients with HVPG more than 10 and those with lower HVPG.

The predictive models diagnoses CSPH in cirrhotic patients based on liver stiffness, platelet count and spleen size (Berzigotti *et al*, 2013), bilirubin (Park *et al*, 2009), palpable spleen, low platelet count, spleen size> 13.8 mm, portal vein>13 mm and splenic vein> 11.5mm (Sarangapani *et al*, 2010), palpable spleen and thrombocytopenia (Sharma *et al*, 2007), prothrombin time, portal vein diameter and splenic width (Hong *et al*, 2011), low platelet count, Child-Pugh class B/C, spleen diameter and platelet spleen diameter ratio 909 (Cherian *et al*, 2011) or PH index and splenic diameter (Tarzamni *et al*, 2008) but none studied such models in HCC patients. Bilirubin level and prothrombin time showed no statistical different, as patients with Child class A compensated cirrhosis, and PH index significantly correlated with HVPG gave accepted likelihood ratio or fitness.

Conclusion

Portal vein diameter ≥ 1.3 cm, mono or biphasic pattern of flow in hepatic veins and Giannini index≤ 909 were 3 parameters in used model for non-invasive prediction of portal hypertension. This model in other patients' groups; cirrhotic without HCC, decompensated cirrhotic patients and cirrhotic patients due to etiologies other than HCV are strongly recommended.

The authors have no conflict of interest.

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