Original Article

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Impact of non-selective beta blockers on portal hypertension and hepatic elasticity in hepatitis C virus-related liver cirrhosis

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Summary **Portal hypertension and its complications are the leading causes of morbidity and mortality in patients with liver cirrhosis. Noninvasive assessment of liver stiffness had been an effective tool for assessment of fibrosis progression in chronic liver disease. It was intended to assess liver stiffness measurement (LSM), portal vein diameter (PVD), splenic bipolar diameter (SD), and the platelet count/spleen diameter (PC/SD) ratio in patients who test positive for the hepatitis C virus (HCV) and to study the impact of non-selective beta blockers (NSBB) on the grade of esophageal varices (EVs) and liver elasticity. Subjects were 80 patients with Child-Pugh grade A or B compensated cirrhosis who tested positive for HCV. All of the patients underwent a laboratory workup including AFP, HCV antibodies, HCV RNA, HBsAg, LSM according to real-time elastography, upper gastrointestinal endoscopy (UGIE) to detect and grade EVs, calculation of the PC/SD ratio, and measurement of the PVD and SD according to real-time abdominal ultrasonography. All patients were given the maximum tolerated dose of NSBB for three months, and UGIE, LSM, PC/SD, PVD, and SD were subsequently reassessed and reported. LSM and the PC/SD ratio were exceptional noninvasive tools for prediction of significant EVs (grade ≥ II, $p < 0.001$) with a sensitivity 82.4% and a specificity 82.6% at a cutoff point 18 kPa for LSM, and a sensitivity 94.1% and specificity 69.6% at a cutoff point 880 for the PC/SD ratio. LSM is highly correlated with PVD, the PC/SD ratio, SD, and the Child-Pugh score. NSBB significantly decreased PVD. The percent change in PVD significantly correlated with LSM, the grade of EVs, and SD. Findings indicated that LSM is a noninvasive, rapid, and reproducible tool with which to detect portal hypertension and EVs. NSBB therapy can effectively decrease PVD and may consequently improve the EV grade with no significant impact on LSM in patients with liver cirrhosis.**

Keywords: Liver stiffness measurement, portal hypertension, esophageal varices, non-selective beta blockers

1. Introduction

Portal hypertension is believed to be the main trigger for most complications in patients with liver cirrhosis. A hepatic venous pressure gradient (HVPG) ≥ 10 mm Hg is necessary for the development of ascites, esophageal varices (EVs), and all other complications of liver cirrhosis (*1*). Clinically significant portal hypertension (CSPH) is invariably found in patients with decompensated liver disease (*2*); its presence is an independent predictor of clinical decompensation in 50-70% of patients (*3*). The presence of EVs, as a complication of CSPH, is an independent predictor of significant morbidity, so all patients with compensated cirrhosis should be screened for the presence of EVs (*4*).

Patients with liver cirrhosis must sometimes undergo invasive procedures to diagnose EVs and CSPH, such as liver biopsy and hepatic vein catheterization. These procedures require specific experience and carry some

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risk, so simple, noninvasive, accurate, and objective diagnostic tools need to be developed for high-risk patients. A reproducible estimation of liver stiffness (LS) according to transient hepatic elastography has been developed as a noninvasive method to diagnose CSPH and EVs in patients with compensated cirrhosis (*5*).

Non-selective beta-blockers (NSBB) have been used since 1981 as a therapeutic option for portal hypertension in patients with liver cirrhosis. Patients with refractory ascites experience a diminished sensitivity to the NSBB due to increased levels of splanchnic pro-inflammatory cytokines; the beneficial effects of NSBBs may decrease, and NSBBs may even be harmful (*6*).

One aim of the current study was to assess hepatic elasticity, portal vein diameter (PVD), the platelet count/spleen diameter (PC/SD) ratio, and spleen bipolar diameter (SD) in patients with compensated liver cirrhosis who were also infected with HCV. A second aim of this study was to examine the impact of NSBB on the grade of EVs and liver stiffness measurement (LSM).

2. Patients and Methods

2.1. *Study design and settings*

A case control, prospective observational study was conducted in the Hepatogastroenterology and Endoscopy units of the Department of Internal Medicine in cooperation with the Advanced Center for Liver Disease of Zagazig University Hospital, Egypt over a six-month period from November 2017 to April 2018.

2.2. *Subject population*

Potential subjects were 300 patients with liver cirrhosis and who were infected with HCV who were seen at an outpatient clinic and who were scheduled for diagnostic upper GI endoscopy. Subjects were 80 patients with compensated cirrhosis who met the inclusion criteria while not meeting the exclusion criteria (Figure 1).

2.3. *Inclusion and exclusion criteria*

Patients had Child-Pugh A or B grade compensated liver cirrhosis and tested positive for HCV infection. Patients infected with the hepatitis B virus or who had hepatocellular carcinoma, portal vein thrombosis, who had undergone sclerotherapy or band ligation to treat EVs, patients who had previously received or who were ineligible to receive NSBBs (obstructive airway disease, peripheral arterial disease, or brittle diabetes), patients who had Child-Pugh grade C cirrhosis, patients

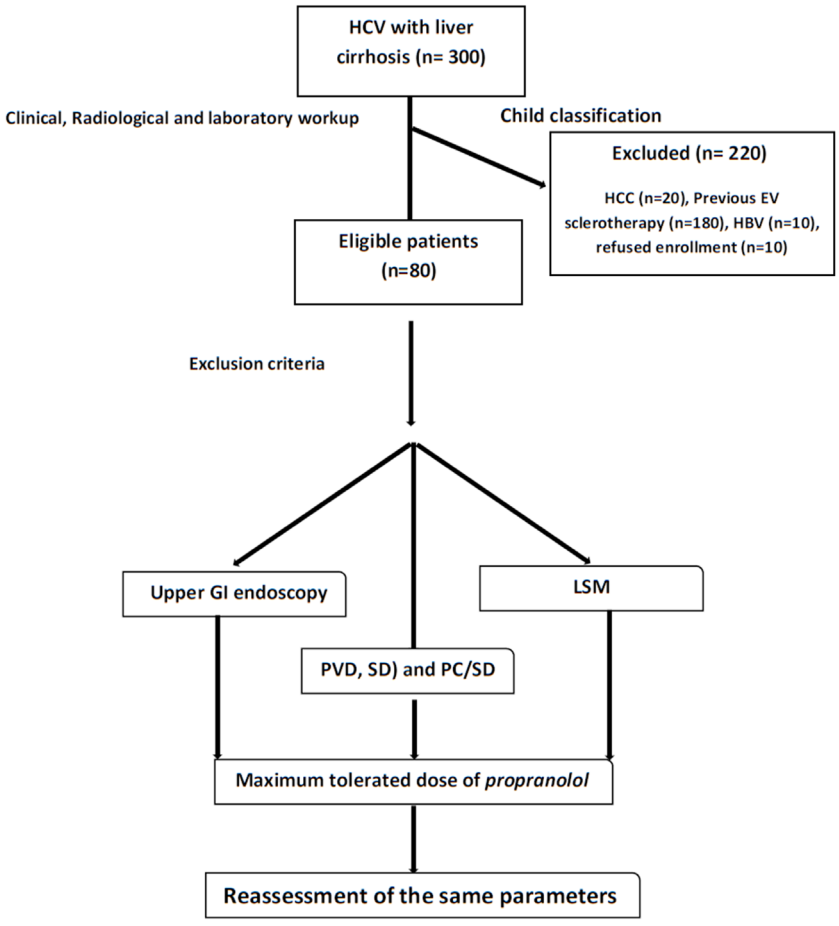

Figure 1. Flowchart for patients in this study.

who did not have EVs, and patients who missed follow-up or who declined to participate in this study were excluded. All of the enrolled patients gave informed consent *via* a form developed by the research team. This study was approved by the ethical committee of Zagazig University. All information gathered from patients was kept confidential.

2.4. *Methods*

All patients had their history taken and underwent a physical examination and laboratory testing that included a complete blood count (CBC), platelet count, liver and kidney function tests, the international normalized ratio (INR), measurement of alpha fetoprotein (AFP), and serum markers for HCV and HBV. PVD and SD had been assessed using trans-abdominal ultrasound (Famio 5 ultrasound Machine, Abex Medical System, Toshiba, Japan). Variations in PVD during respiratory phases were addressed by measuring PVD during inspiration, expiration, and at rest. The normal PVD was less than 13 mm and SD was less than 130 mm. The platelet count (PC) was divided by SD to yield the PC/SD ratio. Upper gastrointestinal endoscopy (UGIE) served as a standard diagnostic modality for EVs. All patients underwent UGIE using GIF- XP160 video endoscopy (Exera 160 series, Olympus Endoscopy System, Japan). EVs were graded into the four grades of I, II, III, and IV according to the modified Paquet classification.

Estimation of liver stiffness using real-time elastography was accomplished by measuring the velocity of elastic shear waves in the liver parenchyma generated by the mechanical push (using a Philips IU22 ultrasound machine). The medium reading of the tissue elasticity was calculated and expressed in kPa. The success rate of the examination was calculated as the ratio of the number of validated measurements made by the machine and the total number of attempted measurements during the same examination. The median value for validated measurements was used to represent liver stiffness (*7*).

All patients had been scheduled to receive the maximum tolerated dose of propranolol that decreases the basal heart rate by 25% but not below 60 beats per minute (*5*). The same patients were re-evaluated after 3 months by measuring UGIE, LSM, PVD, SD, and the PC/SD ratio again.

2.5. *Data processing and analysis*

All calculations were performed using the computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA version 18.0). Data were statistically described in terms of mean ± SD, median and range, or frequencies and percentages when available. The Mann Whitney (U) and Kruskal Wallis tests were used when appropriate. Sensitivity and specificity were used to represent the accuracy of the tests. Receiver operator characteristic (ROC) analysis was used to determine the optimum cutoff value for the diagnostic variables studied. To determine the significant independent predictors for the occurrence and the grade of significant EVs, univariate and multivariate regression models were constructed. *P* values < 0.05 was considered statistically significant.

3. Results

The mean daily dose of propranolol used in the study was 66.95 ± 17 mg (range: 30-80 mg), which caused a significant decrease in the mean heart rate from 79.05 ± 9.02 (range: 60-95 b/m) pre- treatment to 61.15 ± 4.73 (range: 55-71 b/m) post-treatment ($p < 0.001$).

According to endoscopic evaluation pre-treatment, 46 patients (57%) had grade I EVs while 32 (40%) had grade II and only 2 patients had grade III EVs (2.5%). Post-treatment endoscopic examination revealed that 4 patients had no EVs (5%), 42 patients had grade I EVs (52.5%), 32 had grade II EVs (40%) and only 2 patients had grade III EVs (2.5%).

There were no significant changes between pre-treatment and post-treatment values for SD, LSM, and PC/SD ($p = 0.5$, 0.77, and 0.08), but PVD decreased significantly ($p < 0.001$) (Table 1). The percent change in PVD was correlated with the percent change in EV grade, LSM, and SD ($p = 0.05$, 0.001, and 0.05) (Table 2).

Pre- and post-treatment, the grade of EVs was

Table 1. Mean and median values for variables pre-treatment in the patients studied

Variable	Pre-treatment, ($n = 80$)	Post-treatment, ($n = 80$)	Test of sig.	p
PVD: (mm)			t	< 0.001
Mean ± SD	12.8 ± 1.34	11.44 ± 1.93	5.87	
Range	10 – 15	7 - 15		
Splenic diameter: (cm)			t	0.50
Mean ± SD	14.77 ± 2.17	14.8 ± 2.18	0.84	
Range	7.5 – 18.3	7.5 - 18		
LSM: (kpa)			W	0.77
Median (Range)	18.15 (8 – 44.1)	17.6 (7.8 – 43)	0.29	
PC/SD ratio			W	
Median (Range)	800 (188-4667)	720 (226-4440)	1.47	0.08

significantly correlated with PVD, SD, and LSM and inversely correlated with the PC/SD ratio (Table 3). In the pre-treatment evaluation, LSM at a cutoff value of 18 kPa, a PC/SD ratio of 808, and PVD of 12.5 mm predicted EVs (≥ grade II), while LSM at a cutoff value of 16.8 kPa, a PC/SD ratio of 720, and PVD of 11.5 mm post-treatment predicted EVs ≥ grade II, thus indicating the impact of adding NSBB (Table 4). LSM was significantly correlated with both BMI and age ($p < 0.05$ and < 0.001).

The pre- and post-treatment mean values for PVD (12.8 ± 1.34 *vs.*11.44 ± 1.93 mm) differed significantly ($p < 0.001$). PVD at a cutoff value of 12.5 mm had a sensitivity 82.4% and a specificity of 47.8% at predicting significant EVs. PVD was significantly correlated with age and BMI ($p = 0.02$ and 0.001). SD did not change significantly with NSBB (14.77 ± 2.17 cm *vs*. 14.8 ± 2.18, $p = 0.5$) post-treatment. There was no significant correlation between SD and the NSBB dose ($p = 0.88$). The PC/SD ratio was highly inversely correlated with the grade of EVs, PVD, and SD during pre- and post-treatment assessments ($p < 0.001$). The PC/SD ratio was significantly inversely correlated with age and BMI ($p < 0.001$). LSM was highly correlated with the grade of EVs pre- and post-treatment ($p < 0.001$). LSM at a cutoff value 18 kPa had a sensitivity 82.4% and a specificity of 82.6 % at predicting EVs (≥ grade II). The NSBB dose was not significantly correlated with LSM, SD, or the PC/SD ratio but was significantly correlated with the percent change in PVD ($p < 0.001$).

Table 2. Correlation between the percent change in the portal vein diameter (PVD) and the percent change in the grade of esophageal varices, liver stiffness measurement, and splenic diameter in the patients studied

Variable	% change in PVD	
	r	*P*
% change in EV grade	0.33	< 0.05
% change in LSM	0.63	< 0.001
% change in splenic diameter	0.34	< 0.05

4. Discussion

Portal hypertension and its complications are the leading causes of morbidity and mortality in patients with liver cirrhosis. The most important consequences are those that constitute decompensation of cirrhosis, such as ascites, variceal hemorrhage, and encephalopathy. The median survival of a patient without complications of portal hypertension is longer than 12 years, whereas it is shorter than 2 years for a decompensated patient (*1*).

NSBBs are commonly used to decrease portal

Table 3. Correlation between liver stiffness measurements, portal vein diameter, beta blocker dose, grade of esophageal varices, platelet/spleen ratio, and spleen diameter pre- and post-treatment among the patients studied

Variable	PVD ($n = 80$)		BB dose ($n = 80$)		EV grade ($n = 80$)		LSM ($n = 80$)		SD ($n = 80$)	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Pre-treatment										
BB dose	- 0.33	0.02	---	----	---	----	---	----	---	----
EV grade	0.54	< 0.001	- 0.17		---	-----	---	----	---	----
LSM	0.63	< 0.001	0.04	0.83	0.53	< 0.001	---	----	---	----
SD	0.31	0.04	- 0.05	0.77	0.62	< 0.001	0.55	< 0.001	---	----
PC/SD ratio	- 0.49	< 0.001	- 0.11	0.17	- 0.71	< 0.001	- 0.62	< 0.001	- 0.79	< 0.001
Post-treatment										
BB dose	- 0.02	0.90								
EV grade	0.42	0.007	- 0.19	0.25	----	----				
LSM	0.67	< 0.001	- 0.05	0.75	0.49	< 0.001				
SD	0.25	0.12	- 0.03	0.88	0.28	0.08	0.61	< 0.001	----	----
PC/SD ratio	- 0.51	< 0.001	- 0.19	0.23	- 0.53	< 0.001	- 0.63	< 0.001	- 0.79	< 0.001

Table 4. Validity of cutoff values for liver stiffness measurement, the platelet/spleen ratio, and portal vein diameter in diagnosis of esophageal varices pre- and post- treatment

Test	Sensitivity	Specificity	PPV	NPV	Kappa	*p*
Pre-treatment						
LSM > 18 kPa	82.4	82.6	77.8	86.4	0.64	< 0.001
PC/SD ratio ≤ 880	94.1	69.6	69.6	94.1	0.61	< 0.001
PV > 12.5 mm	82.4	47.8	53.8	78.6	0.28	0.04
Post-treatment						
LSM > 16.8 kPa	90.9	62.5	52.6	93.8	0.45	< 0.003
PC/ SD ratio ≤ 720	90.9	62.5	52.6	93.8	0.45	< 0.003
PV > 11.5mm	72.7	62.5	47.1	83.3	0.31	< 0.05

hypertension in patients with compensated cirrhosis in order to facilitate primary and secondary prevention of first variceal bleeding. Propranolol is the most commonly used NSBB that causes a significant reduction in portal pressure. The current study used propranolol at a dose that achieved a 25% reduction in heart rate. In patients with high-risk varices, an NSBB significantly decrease the incidence of first variceal hemorrhage.

In patients who have already bled from varices, an NSBB prevented the recurrence of variceal hemorrhage when used in combination with endoscopic variceal therapy. Recent data suggested that in patients with compensated cirrhosis (*i.e.*, patients who have CSPH with no or small varices), NSBB provides protection from clinical decompensation (*8*).

In the current study, females tended to have a lower PC/SD ratio and PVD but higher LSM. These findings agreed with the results of Castera *et al*. (*9*) regarding a non-significant difference between genders. In the study by Castera *et al*., SD and PVD were significantly correlated with age, and the PC/SD ratio was significantly inversely correlated with age.

The current study found that age was correlated with LSM, but Castera *et al*. (*9*) reported that the two were not significantly correlated. The current study found that LSM was correlated with BMI, and this finding agrees with the results of Castera *et al*. (*9*) and Das *et al*. (*10*); in the latter study, the mean value for LSM was higher in obese individuals compared to that in individuals with a normal BMI.

Few studies have discussed the impact of NSBBs on LSM, but Razavi *et al*. (*2*) studied the correlation between HVPG and LSM before and after NSBB administration, and they concluded that the two were more strongly and directly correlated post-treatment than pre-treatment.

The correlation between LSM and HVPG improved in hemodynamic responders to NSBBs (R = 0.864) but not in non-responders (R = 0.535), whereas changes in LSM, heart rate, and mean arterial pressure were similar in both groups (*11*).

Pre-treatment values for LSM at a cutoff point of 18 kPa had a sensitivity of 82.4% and a specificity of 82.6% at detecting significant EVs (≥ grade II). Accordingly, LSM is an exceptional test with which to predict the presence of significant EVs. However, other studies used different cutoff values for large EVs. A study by Sporea *et al*. (*12*) reported that a cutoff value of 24.8 kPa had a sensitivity of 81% and a specificity of 80.7%, but that study was a retrospective study, and it did not record LSM in real time or whether patients were given NSBBs or not.

Kazmi *et al*. (*13*) conducted a study using cutoff value less than 19 kPa and found that this value was highly predictive for the absence of grade II EVs (sensitivity of 84%, specificity of 78%, PPV of 47%, and NPV of 93%). Francesco *et al*. (*14*) found that LSM at a cutoff value of 17.6 kPa had a sensitivity of 90%, a specificity of 86%, and an NPV of 66% at predicting EVs. Results of both of those studies agreed with the current results. These variations in cutoff values for LSM to detect or rule out EVs may be related to many factors that include the type of patient, sample size, and different etiologies of cirrhosis.

The current study found that LSM was significantly correlated with the Child-Pugh grade during both pre- and post-treatment assessments. This finding agreed with the results of Razavi *et al*. (*2*), Castera *et al*. (*9*), and Foucher *et al*. (*15*), who all reported that LSM was correlated with the Child-Pugh score as well as with the stage of fibrosis and EV grade.

The mean PVD decreased significantly after 3 months of therapy with propranolol. With PVD as a noninvasive predictor for EVs, PVD of 12.5 mm pre-treatment can be used as a cutoff point to predict significant EV with a sensitivity of 82% and a specificity of 47.8%. Schepis *et al*. (*16*) found that PVD of 13 mm is a cutoff value for the presence of EVs.

The PC/SD ratio is considered to be another noninvasive marker for the presence of EVs. In the current study, a PC/SD ratio at a cutoff of 880 had a sensitivity of 94.1% and a specificity of 69.6% at predicting significant EVs. Baig *et al*., (*17*) found that a PC/SD ratio at a cutoff point of 890 was a predictor of EVs with a PPV of 95.5% and NPV of 95.1%, while Giannini *et al*. (*18*) found that a PC/SD ratio at a cutoff point of 909 predicted EVs with a sensitivity of 100% and a specificity of 71%. The mean value for SD did not change significantly after treatment with NSBBs.

One limitation of the current study was that it did not measure HVPG since doing so would be invasive. Instead, this study evaluated the grade of EVs, which are a common complication of a significant increase in HVPG.

In conclusion, LSM is a noninvasive, reproducible, and rapid method with which to evaluate liver cirrhosis and the stage of fibrosis and with which to evaluate the grade of either small or significant EVs. NSBB therapy can effectively decrease PVD and may consequently improve the EV grade with no significant impact on LSM in patients with liver cirrhosis.

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