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Correlation of spleen stiffness measured by Acoustic Radiation Force Impulse Imaging (ARFI) with Hepatic Venous Pressure Gradient (HVPG) in the prediction of esophageal varices (EVs) grades in cirrhotic patients

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Abstract---Background: measurement of spleen stiffness (SS) by ARFI may predict the presence of EVs. Aim: To assess the correlation of SS measured by ARFI as noninvasive assessment with HVPG in the prediction of presence and grades of EVs in cirrhotic patients. Methods: 30 patients with post HCV liver cirrhosis who underwent biochemical tests, abdominal ultrasound (US) , Doppler , Upper gastrointestinal endoscopy (UGE), liver stiffness (LS) and spleen stiffness (SS) measurements using ARFI elastography and HVPG. Results: statistically significant difference was found between EVs presence and grades in relation to HVPG. In contrary no statistically significant difference was found between EVs presence and grades in relation to SS. Conclusion: HVPG had good significant positive correlation with presence and grades of EVs. There was no significant correlation between non-invasive parameters including the SS and LS (by ARFI) and presence or grades of EVs. There was no significant correlation between HVPG and SS and LS (by ARFI).

Keywords---Spleen stiffness, ARFI, liver cirrhosis, HPVG, Esophageal varices.

Introduction

Portal hypertension (PH) is common sequelae of liver cirrhosis, leading to the EVs development, which is considered the most dangerous complication. HVPG is considered the optimal method for PH assessment ([Garcia-Tsao et al., 2017](#)). To diagnose clinically significant EVs, screening by periodic upper endoscopy should be done. However, repeated endoscopies are expensive and may be refused by many patients. So, we should find out a non-invasive and cheap technique to predict EVs presence and risky EVs ([Şirli et al., 2015](#)).

The Baveno VI criteria recommended using LS measurement less than 20 kPa by transient elastography (TE) and PLT count more than $150 \times 10^9/L$ for excluding risky EVs in compensated cirrhotic patients ([De Franchis, 2015](#)). Splenic congestion which occur secondary to PH leads to architectural changes in the splenic arteries and veins and this results in the spleen fibrosis and consequently increase in SS. Different elastographic ways to assess SS including shear wave elastography (SWE), TE and ARFI. ARFI is preferred for SS measurement because it is not affected by ascites presence or obesity ([Attia et al., 2015](#)). It was reported that ARFI SS is considered an ideal method clinically for screening of EVs in cirrhotic patients. Also by easily diagnosing risky EVs, ARFI can differentiate variceal bleeders from non-bleeders ([Braticevici et al., 2019](#)). Our aim is to assess the correlation of SS measured by ARFI as non-invasive assessment with HVPG in the prediction of presence and grades of EVs in cirrhotic patients.

Patients and Methods

Thirty patients with post HCV liver cirrhosis were included in this prospective study. This study was conducted in Hepato-gastroenterology and Intervention Radiology Departments in Theodor Bilharz research institute (TBRI) and Cairo

University Center for hepatic fibrosis (CUC HF); funded by STDF (5274 center of excellence) in the faculty of medicine, Cairo University.

Adults with HCV related Liver cirrhosis were included in the study.

The following patients were excluded:

- 1) Patients with HCC
- 2) Patients with previous variceal bleeding.
- 3) Patients how have been treated with beta blockers or nitrates, or endoscopic band ligation or injection sclerotherapy of EVs.
- 4) Pregnant patients.
- 5) Patients with thrombosis of spleno-portal axis.
- 6) Serum creatinine more than 2 mg/dl.
- 7) INR more than 1.7 and platelet count less than 50000/mm³ (Patel et al., 2012).
- 8) Splenctomized patients

All included patients were evaluated by the following: -

1- *History taking: with special stress on the following:*

- a- Symptoms of decompensated liver cirrhosis as hepatic encephalopathy, bleeding tendency, hematemesis or melena.
- b- Previous documented history of upper GI endoscopic examination or doing any therapeutic endoscopic intervention.
- c- Use of beta blocker or nitrate drugs.
- d- Previous history of splenectomy.
- e- History of shistosomiasis.

2- *Clinical Examination: with special emphasis on:*

- a- Conscious level.
- b- Vital signs (pulse and blood pressure).
- c- Signs of decompensated liver cirrhosis as jaundice, ascites, palmer erythema and lower limb edema.
- d- Hepatomegaly or splenomegaly.

3- *Laboratory investigations:*

- Complete blood picture.
- Biochemical profile including hepatic and kidney function tests.
- HCV Ab and HBs Ag.

4-*Noninvasive parameters and scores:*

- ARFI-spleen diameter to platelet ratio score (ASPS): ARFI velocity LS (m/s) × spleen diameter (mm)/plt count (×103/mm³) was measured to be correlated with EVs (Park et al., 2015).
- Portal hypertension risk score = -5.953 + 0.188 x LS + 1.583 x sex (1: male; 0: female) + 26.705 x spleen diameter (cm)/platelet count (×103/mm³) ratio and varices risk score = 4.364 + 0.538 x spleen diameter (cm) - 0.049 x plt count (×103/mm³) - 0.044 x LS + 0.001 x (LS x plt count) were evaluated (Berzigotti et al., 2013).
- We constructed a possible ARFI-based prediction models by using the following variables (plt count, SS, LS and splenic vein diameter (SVD)), where these variables were put in these equations (platelet count/SS ratio, SS x SVD/plt

count ratio and LS x SVD/plt count ratio) to be correlated with EVS and HVPG.

5-Abdominal ultrasonography and Doppler study:

6-Upper GIT endoscopy:

The grades of EVs were categorized into three grades (Grade I to III) by using the criteria proposed by the Japanese Research Society for PH ([deFranchis, 2016](#)).

7-Acoustic Radiation Force Impulse (ARFI) elastography:

ARFI Elastography was performed by with a Siemens ACUSON S3000 Ultrasound System (Siemens AG, Erlangen, Germany) with a 6C1 HD transducer, by using Virtual Touch Tissue Quantification application for measuring LS and SS. 10 valid measurements were aimed for every patient where the mean value of these valid measurements was calculated and expressed in (meters/second - m/s) ([Bota et al., 2011](#)).

8-HVPG measurement

The HVPG is calculated by subtracting free hepatic venous pressure (FHVP) (which reflects intra-abdominal pressure) from wedged hepatic venous pressure (WHVP) (which reflects portal venous pressure), where these values are gained by right hepatic vein catheterization. The FHVP was obtained by direct assessment of pressure in the hepatic vein. The WHVP was obtained by balloon occlusion of the hepatic vein or by wedging the catheter in the end tributaries of a hepatic vein. The balloon occlusion technique is preferred because the pressure from large portion of the liver can be measured ([Berzigotti et al., 2013](#)).

Statistical analysis

Data were analyzed using Stata® version 14 (StataCorp LLC, College Station, TX, USA). Normality of numerical data distribution was examined using the Shapiro-Wilk test. Normally distributed numerical variables were presented as mean ± SD and intergroup differences were compared using the unpaired t test (for two-group comparison) or one-way analysis of variance (ANOVA) (for multiple-group comparison). The Tukey-Kramer post hoc test was applied when ANOVA revealed a statistically significant difference among the groups.

Categorical variables were presented as number and percentage and intergroup differences were compared using Fisher's exact test (for nominal data) or the chi-squared test for trend (for ordinal data). Correlations were tested using the Pearson correlation or Spearman correlation as appropriate. Receiver-operating characteristic (ROC) curve analysis was used to examine the predictive value of numerical variables.

Results

Demographic, laboratory, ARFI quantitative data, other noninvasive scores and HVPG characteristics of the study populations are represented in (Table 1).

EGD was done and showed that 25 patients (83%) had varices, divided into: 13 patients (43%) with varices grade III, 6 patients (20%) with varices grade II and 6

patients (20%) with varices grade I, while 5 patients (17%) had no varices. There was statistically significant difference between presence and absence of EVs, regarding HVPG, where HVPG was higher in patient with EVs, but there was no statistically significant difference between presence and absence of EVs regarding liver and spleen stiffness (by ARFI) (Table 2).

There was statistically significant difference between different grades of EVs regarding HVPG, where HVPG was higher in Patients with EVs grade III, but there was no statistically significant difference between different grades of EVs regarding liver and spleen stiffness (by ARFI) (Table 3).

Our results showed that there was no statistically significant difference between presence and absence of EVs, Also between their different grades regarding the other noninvasive scores. Even with the constructed a possible ARFI-based prediction models by using the following variables (plt count, SS, LS and SVD), where these variables were put in these equations (plt count/SS ratio, SS x SVD /plt count ratio and LS x SVD/plt count ratio) to be correlated with EVs and HVPG. We cannot found statistically significant difference between presence and absence or different grades of EVs.

There was no statistically significant correlation between all non-invasive scores & HVPG (table 4). Cut off value for HVPG was put at 10 mmHg (the level of clinical significant portal hypertension) and the correlations were statistically done with all parameters showed that there were statistically significant positive correlations with presence and grades of EVs (p value 0.000 and 0.003 respectively) (Table 5)

Table (1): Characteristics of the studied patients (n = 30).

Characteristics	Range(Mean±SD)/Number
Age(yrs.)	45 – 65/53.93±4
Sex	Male 18
	Female 12
Platelet count (x103/mm3)	98.7±32.2
PC	76.05±13.14
INR	1.23±0.15
AST(IU/L)	86.83±43.84
ALT(IU/L)	54.70±34.36
Bilirubin(mg/dl)	1.26±0.61
Albumin(g/dl)	3.30±0.71
Creatinine(mg/dl)	0.85±0.18
Liver stiffness (m/s)	1.87 – 4.24/2.81±0.58
Spleen stiffness (m/s)	2.17 – 4.21/3.44±0.57
ARFI-spleen diameter to platelet ratio score (ASPS)	5.11±2.09
PH risk score	0.54±0.32
Varices risk score	0.48±0.32
HVPG(mmHg)	9.00 – 30.00/17.52±6.57

Table (2): The comparison between presence and absence of EVs as regard to liver and spleen stiffness (by ARFI) and HVPG (n=30).

Variable	Absence of EVs (n=5)		presence of EVs (n=25)		p-value
	Mean	SD	Mean	SD	
Hepatic ARFI (m/s)	2.66	0.92	2.83	0.52	0.553
Splenic ARFI (m/s)	3.43	0.77	3.45	0.54	0.957
HVPG (mmHg)	12	4	19	6	0.034

Table (3): The comparison between the different grades of EVs as regard to liver and spleen stiffness (by ARFI) and HVPG (n=30).

Variable	No EVs (n=5)		Grade I EVs (n=6)		Grade II EVs (n=6)		Grade III EVs (n=13)		p-value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Hepatic ARFI (m/s)	2.66	0.92	3.06	0.73	2.64	0.45	2.82	0.42	0.611
Splenic ARFI (m/s)	3.43	0.77	3.46	0.54	3.09	0.48	3.61	0.52	0.343
HVPG (mmHg)	12	4	15	5	15	2	22	5	0.001

Table (4): The correlation of the noninvasive scores with HVPG (n=30).

Variable	HVPG		
	R	p value	Significance
Splenic ARFI	0.343	0.093	NS
Heptic ARFI	0.035	0.870	NS
ASPS	0.256	0.216	NS
PH risk score	0.204	0.328	NS
Varices risk score	0.190	0.362	NS
SS x SVD/ platelet count	0.15	0.5	NS
LS x SVD/ platelet count	0.30	0.1	NS

Table (5): The correlation of all parameters with HVPG at cut off 10 mmHg (n=30).

Variable	HVPG (Cut off value at 10 mmHg)		
	R	p value	Significance
Presence of EVs	0.846	0.000	S
Grade of EVs	0.568	0.003	S
Splenic ARFI	0.137	0.515	NS
Heptic ARFI	0.111	0.597	NS
APRI score	0.324	0.114	NS
ASPS	0.034	0.871	NS
PH risk score	0.085	0.685	NS
Varices risk score	-0.084	0.688	NS

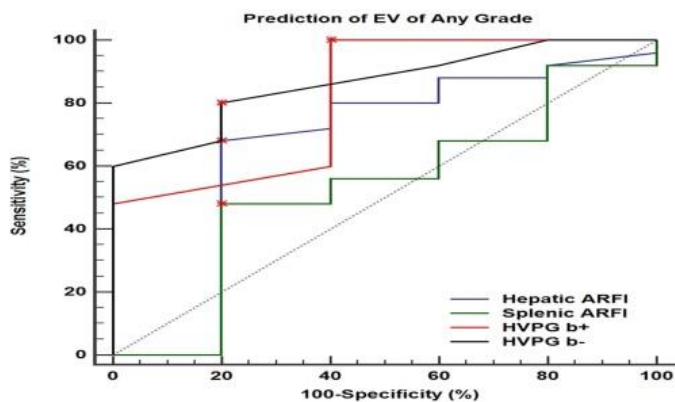


Figure (1) shows (ROC) curve for prediction of presence of EVs using ARFI and HVPG (n=30).

HVPG was found as good significant predictor of grade 111 EVs (p value < 0, 0001).

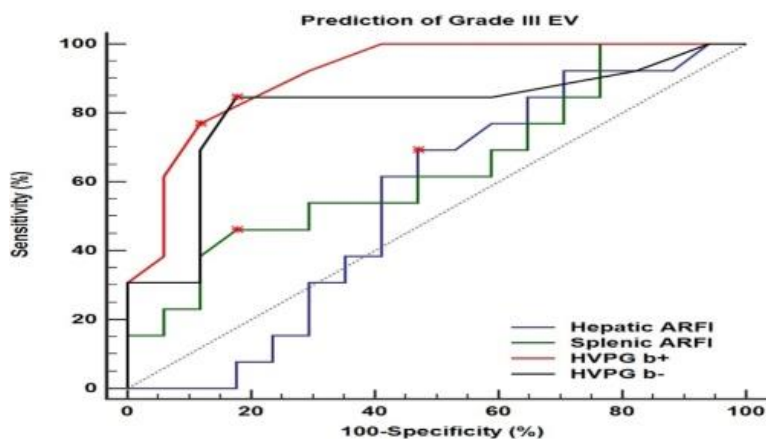


Figure (2) shows (ROC) curve for prediction of grade III using ARFI or HVPG. HVPG was found as good significant predictor of EVS of any grade (p value 0,004).

Discussion

Zykus et al. (2015) predicted that SS might be more precise than LS for HVPG evaluation because the dynamic component of PH is reflected by SS. Our study showed that there were no statistically significant difference between presences or absence and between different grades of EVs regarding SS by ARFI. We found that SS failed to have predictive value for detection of presence of EVs where the cut off value was ≤ 3.29 , giving 48 % sensitivity and 80 % specificity. Also, SS had poor predictive value for detection of grade III EVs where the best cut off value was >3.94 , giving 46.2 % sensitivity and 82.4 % specificity with AUC = 0.640. This result was in agree with the study done by Bota et al. (2010), where 82 subjects were evaluated, found that there is no significant differences between presence and absence of EVs and also between patients with and without risky bleeding EVs as regard to SS by ARFI . In a study done by Mori et al. (2013), on HCV cirrhotic patients, found that SS measured by ARFI did not differ between the

groups with and without EVs. Moreover, [Park et al. \(2016\)](#), found that SS by ARFI was not reliable for prediction of EVs with no clear explanation and this study was done on 100 patients with alcohol induced liver cirrhosis.

Against our result, SS measurement using ARFI in 340 cirrhotic patients (most of them were HCV positive) was effective in detecting EVs and in predicting the presence of high-risk EVs ([Takuma et al., 2013](#)). [Peagu et al. \(2019\)](#), found that SS measured using ARFI is an excellent method for detecting EVs and diagnosing large EVs in patients with virus-related cirrhosis.

Another study done by [Kim et al. \(2015\)](#) on 125 cirrhotic patients, found that SS by ARFI was significantly higher in patients with EVs than in patients without EVs. [Ferreira et al. \(2016\)](#), reported that the group of patients with EVs had splenic-ARFI higher than 2.96 (± 0.53) m/s, but the group of patients without EV had splenic-ARFI lower than 2.11 (± 0.52) m/s.

Moreover, [Bota et al. \(2012\)](#), detected a positive association between different grades of EVs and SS measurement by ARFI in patients with various etiologies. Our study showed that there were no statistically significant difference between presences or absence and between different grades of EVs regarding LS by ARFI. We found that LS had poor predictive value for detection of presence of EVs where the best cut off value was >2.63 , giving 68 % sensitivity and 80 % specificity. LS failed to have predictive value for detection of grade III EVs where the best cut off value was > 2.66 , giving 69.2 % sensitivity and 52.9 % specificity. This was in agree with a study done by [Peagu et al. \(2019\)](#), who found that LS was not correlated with the presence of EVs or large EVs. Also, study done on 74 HCV cirrhotic patients where EVs were found in 34 patients not succeeded to find association between LS by ARFI and EVs .¹⁴ Study published by [Şirli et al. \(2010\)](#) on 157 patients, found that no significant difference between presence and absence of EVs and also between small and large EVs as regard to LS measured by ARFI.

Moreover, [Ye et al. \(2012\)](#) reported that there was no association between LS by ARFI and EVs grades. Also, in a study done by [Mori et al. \(2013\)](#) found that the LS measured by ARFI in HCV patients did not differ between the groups with and without EVs.

In contrast to our study, the study of [Morishita et al. \(2014\)](#) on 135 cirrhotic patients where all of them were HCV positive, Showed that the LS by ARFI had positive correlation with the EV grades.

This discrepancy due to EVs are one of the collateral circulation and represent only a part of PH ([Mori et al. 2013](#)). Also, this may attributed to small sample size in our study as compared with other studies. In addition, most of our patients have EVs (25 patients 83%) and this made the relation between ARFI and presence of varices statistically insignificant. As regard to etiology of cirrhosis, our study did on HCV only while most of other studies recruited patients of various etiologies.

In this study, we found that there was no significant association between SS and HVPG or HVPg at cut off 10 mmHg.

This result was in agreement with [Elkrief et al. \(2015\)](#) who found no significant differences among groups analyzing CSPH regarding SS measured by TE and shear wave elastography (SWE). Also, [Zyklus et al. \(2015\)](#) reported that insufficient accuracy of SS by TE may be explained by development of various shunts which are formed during progression of PH. Also, in the study done by [Sharma et al. \(2013\)](#), they found that SS by TE was not associated with the HVPG in the group of 24 patients with HVPG \geq 19 mm Hg.

On the other hand, the study published by [Dvorak et al. \(2014\)](#) on 25 cirrhotic patients of multiple etiologies found that SS by ARFI significantly correlated with HVPG. Also [Borghi et al. \(2012\)](#), found a good correlation between SS measured by ARFI and HVPG in study done on 40 cirrhotic patients of various etiologies. Moreover, SS measurement by ARFI was significantly higher in patients with HVPG of high values than in patients with HVPG of low values ([Attia et al. 2015](#)). This difference between our results and these of other studies could be explained by variability of SS according to the degree of HVPG and the presence or absence of EVs and its grade. Needless to say that the etiology of liver disease affects the results. All our patients have cirrhosis and PH due to HCV while most of other studies recruited patients of various etiologies.

In this study, we found that there was no significant correlation between LS and HVPG or HVPg at cut off 10 mmHg. This result was in agree with the study which found that LS by ARFI did not correlate with HVPG ([Dvorak et al. 2014](#); [Borghi et al., 2012](#)). In another study, LS by fibroscan showed no correlation with HVPG ([Sharma et al., 2013](#)). Similarly, LS measurement by TE was insufficient accurate for predicting patients of HVPG more than 12mmHg and also had poor prediction for EVs. Thus, LS is not considered as effective as HVPG with respect to overall diagnostic accuracy ([Carrion et al., 2006](#); [Kazemi et al., 2006](#); [Castéra et al., 2009](#)). [Castera et al. \(2012\)](#). [Vizzutti et al. \(2007\)](#) and [Reiberger et al.\(2012\)](#) found that the correlation between LS by TE and HVPG had lost the linearity for HVPG values more than 12 mmHg.

Against our results, LS measurement by ARFI was significantly higher in patients with HVPG of higher values than in patients with HVPG of lower values ([Attia et al., 2015](#)). Another study found that LS measured ARFI was well correlated with PH ([Salzl et al., 2014](#)). Also, [Procopet et al. \(2015\)](#) found that LS measured by SWE has a good correlation with HVPG.

[Colecchia et al. \(2012\)](#) found that LS measured by fibroscan has the strongest positive correlation with HVPG than the other noninvasive tests. Our results may be explained by in late stages of cirrhosis, The PH becomes independent from the increased hepatic resistance (which is assessed by LS), but there are extra hepatic components which are more obvious such as (hyper dynamic circulation, peripheral vasodilatation and splanchnic vasodilatation) ([Vizzutti et al.,2007](#), [Reiberger et al., 2012](#)). [Castera et al.\(2012\)](#) found that clinical significant PH and EVs formation occur with HVPG values which exceed 10-12 mmHg and this explain why PH occur independent from liver cirrhosis,. Accordingly, the LS

measurement is not precise for the prediction EVs presence and grades, this is applied to our study as the most of our patients have HVPG > 10.

In our study, we found that there were statistical significant positive correlation between HVPG at cut off 10 mmHg and endoscopic findings as regard to presence and grade of EVs. We found that the best cut-off level for prediction of presence of EVs was >10 mmHg , giving a sensitivity 100% and specificity 60% (good predictive value) , As regard to prediction of grade III EVs, the best cut off level was > 17, giving a sensitivity 76.9% and specificity 88.2% (excellent predictive value) . This was in agree with [Lee et al. \(2016\)](#), who found that HVPG showed a positive correlation with the EVs grades. Also, [Wadhawan et al. \(2006\)](#); [Kim et al. \(2008\)](#); [Silkauskaite et al. \(2009\)](#) and [Gulzar et al. \(2009\)](#) demonstrated a positive relationship between HVPG and EVS grades.

On the contrary, [Patch et al. \(1999\)](#), found that HVPG did not correlate with EVs grades, their study differs from those published previously where their patients group were different in cause of cirrhosis. Also, [Pemier-Layrargues et al. \(1985\)](#) failed to found correlation between EVs grades and HVPG.

There are some limitations to the current study. Firstly, it was carried out on relatively small number of subjects, thus more studies on larger groups of patients with different etiologies of cirrhosis are needed to confirm these results. Secondly, only five patients had no varices and this made the comparison between presence or absence of EVs as regard to most of other parameters statistically insignificant.

Conclusion

HVPG had good significant positive correlation with presence and grade of EVs. There was no significant correlation between the non-invasive parameters and scores including the SS and LS (by ARFI) and presence or grade of EVs. There was no significant correlation between HVPG and non-invasive parameters and scores including the SS and LS (by ARFI).

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