Original article

Correlation of splenic ARFI with endoscopic findings of esophageal varices in chronic liver parenchymal disease

[1]Viyannan Maheswaran, [2]R. MuthuSubramanian, [3]Rathnasamy Rajakumar, [4]Balalakshmoji Devanand, [5]Leelakrishnan Venkatakrishnan

[1]DNB (RD), PDCC, Assistant Professor, Dept of Radiology.
[2]MD(RD), Senior Resident, Dept of Radiology.
[3]DMRD, DNB (RD), Associate Professor, Dept of Radiology.
[4]MD (RD), Professor, Dept of Radiology.
[5]DM(Gastroenterology), Professor, Dept of Gastroenterology.
PSG Institute of Medical Sciences and Research, Peelamedu, Coimbatore.
Corresponding author: Viyannan Maheswaran, DNB (RD), PDCC, Assistant Professor, Dept of Radiology.

Abstract:

Background: Variceal bleed the major cause of mortality in cirrhosis. Upper gastrointestinal (GI) endoscopy remains the main stay of diagnosis and treatment in variceal bleed. Splenic elastography using Acoustic Radiation Force Impulse (ARFI) technique can be used to non-invasively predict presence and severity of esophageal varices.

Material and methods: It is a hospital based prospective case control study, done in 100 patients with chronic liver parenchymal disease, who had undergone upper GI endoscopy. Fifty consecutive patients with esophageal varies and 50 consecutive patients without esophageal varices were included in the study and subjected to splenic ARFI. Data was analyzed with SPSS version 20.0 software using chi-square test or Fischer exact test, independent sample-t test. The receiver operating characteristics (ROC) curve was plotted and the area under the curve was used to determine the cut off points for statistically significant variables.

Results: Spleen ARFI showed significant correlation between cirrhotics with esophageal varices and without varices groups. The cut off of ≥ 3.16 m/s (AUROC: 0.906) precisely detects varices with sensitivity of 94% and specificity of 92%. Spleen ARFI also correlates with severity of varices. Cut off of ≥ 3.29 m/s (AUROC: 0.874) can confidentially differentiate low grade from high grade varices in cirrhotics with sensitivity of 85% and specificity of 100%.

Conclusions: Amongst the noninvasive parameters analyzed in this study, spleenic ARFI exclusively showed highest sensitivity and specificity in the detection of varices and differentiation of high grade varices from low grade varices.

Key words: Splenic ARFI, cirrhosis, Endoscopy, Esophageal varices.

Introduction:

Diverse insults on the liver lead to a common endpoint as cirrhosis. Cirrhosis is pathologically characterized by extensive fibrosis, regenerative nodules and distortion of hepatic parenchymal architecture [1]. Alcoholism and viral hepatitis have been the most common etiologies leading to cirrhosis, however nonalcoholic fatty liver disease is emerging as an important underlying pathology.

Complications of cirrhosis can be categorized as portal hypertension related and portal hypertension unrelated complications. Most common portal hypertension related complications is development of esophageal varices and variceal bleeding [2]. Till date, invasive upper gastrointestinal endoscopy (UGI scopy) remains the mainstay

www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858

for the detection and grading of esophageal varices [3]. In addition to diagnostic advantage, UGI scopy plays a major role in treatment such as band ligation and sclerotherapy. Despite its diagnostic and therapeutic utility, UGI scopy is an invasive procedure, has its inherent complications such as bleeding, perforation, infection and cardio-respiratory complications related to sedation [4].

With current advances in the field of Ultrasonography, estimation of elasticity of the tissue has been made possible with Elastography. It is analogous to manual palpation and in fact offers better information, based on the principle that pathology changes the stiffness of the tissue. Shear Wave Elastography (SWE) is a technique of elastography that uses "shear wave" generated within tissue secondary to the acoustic push, the so called Acoustic Radiation Force Impulse (ARFI). In this technique as no external compression is required and a push impulse can be directed anywhere, it is possible to attain a fine elastogram of entire organ. Additionally, quantification of elasticity of particular region of interest based on shear wave velocity (SWV) is possible [5].

Elasticity of the spleen will be decreased in cirrhosis due to portal venous congestion and hyperplasia of splenic tissue; hence the splenic stiffness will be increased. Portal venous congestion results in esophageal varices. Screening UGI scopy is recommended in all cirrhotic patients in accordance with recent guidelines as primary prophylaxis against variceal hemorrhage[6]. Implementing these guidelines is confronted with cost, complications and invasiveness of UGI scopy. Hence, it necessitates accurate and noninvasive methods for detecting and grading the severity of esophageal varices.

Aim:

To evaluate splenic ARFI as a noninvasive tool for detection of esophageal varices and grading of varices as to high and low grades in chronic liver parenchymal disease.

Materials and methods:

It is a prospective case control study done on 100 patients over a period of 14 months, who were referred to the department of radiology with a diagnosis of chronic liver parenchymal disease. Subsequently all these patients underwent UGI scopy and were divided into two groups. Consecutive 50 patients without esophageal varices comprised the first group and 50 patients with esophageal varices comprised second group. Study was undertaken after obtaining necessary clearance from the institutional human ethics committee. Patients who are of less than 18 years of age and who did not undergo UGI scopy were excluded from the study. All the patients were subjected to splenic ARFI and UGI scopy.

Splenic ARFI protocol:

Splenic ARFI was performed with Siemens Acuson S2000^{TM} / Siemens Acuson S3000 ^{TM} ultrasound systems with ARFI enabled 6C1 / 4C1 curvilinear transducers. Patient was made to lie in right lateral decubitus position and assessment was done by intercostal approach. In order to cover uniformly the spleen, we adopted the stratified random sampling method used in the previous studies [7] (Figure 1). Spleen will be subdivided into cranial external(1), cranial central(2), cranial internal(1), intermediate external(1), intermediate central(1), intermediate internal(1), caudal external(1), caudal central(1) and caudal internal(1) segments. Numbers in the parenthesis represents the number of ARFI values obtained in each segment. In breath hold position, region of interest measuring 10mm in depth and 5mm in width was placed in parenchyma devoid of visible blood vessels and >1 cm below the level of spleen capsule and ARFI evaluation was done (Figure 2). Total of 10 successful measurements were obtained for each patient. Mean ARFI values were automatically calculated and expressed

www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858

in meters per second (m/s).

The data obtained was coded and entered in Microsoft Excel Spreadsheet. Data was analyzed using SPSS version 20.0 statistical software. Categorical variables were expressed as percentages and the comparative analysis was done using chisquare test or Fischer exact test. Continuous variables were expressed as mean ±standard deviation (SD) and the comparative analysis was done by independentsample 't' test. The receiver operating characteristics (ROC) curve was plotted and the area under the curve was determined to the cut off points for statistically significant variables. A probability value (p value) of less than or equal to 0.05 at 95% confidence interval was considered as statistically significant.

Various radilogical parameters like liver size, portal vein diamater, portal vein flow velocity, spleen size, liver ARFI and splenic ARFI were analysed for their value as predictors of presence or absence of esophageal varices, if present, to differentiate high grade varices from low grade varices using various statistical methods as mentioned above.

Results:

TABLE 1: SEX DISTRIBUTION

SEX	WITH EVs		WITHOUT EVs	
	NUMBER	%	NUMBER	%
MALE	36	72	38	76
FEMALE	14	28	12	24
TOTAL	50	100	50	100

TABLE 2: ETIOLOGY DISTRIBUTION IN CIRRHOTICS WITH EVs

ETIOLOGY	WITH EVs		WITHOUT EVs	
	NUMBER	%	NUMBER	%
ALCOHOL	37	74	35	70
NAFLD	6	12	6	12
AUTOIMMUNE	6	12	9	18
METABOLIC	1	2	0	0
TOTAL	50	100	50	100

www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858

TABLE 3: SIGNIFICANCE OF RADIOLOGICAL PREDICTORS BETWEEN CIRRHOTICS WITH EVs AND WITHOUT EVs

PREDICTOR	INDEPENDENT 't' TEST		
	WITH EVs MEAN ± SD	WITHOUT EVs MEAN ± SD	P value
LIVER SIZE	140.50 ± 20.97	138.36 ± 19.62	0.599
PORTAL VEIN DIAMETER	12.54 ± 2.46	12.28 ± 2.06	0.569
PORTAL VEIN FLOW VELOCITY	18.91 ± 6.23	20.28 ± 4.56	0.216
SPLEEN SIZE	**147.54 ± 26.5**	**138.66 ± 16.90**	**0.049***
PLATELET COUNT SPLEEN SIZE RATIO	**588.52 ± 274.58**	**972.86 ± 177.99**	**0.000***
LIVER ARFI	3.03 ± 0.78	2.92 ± 0.69	0.458
SPLEEN ARFI	**3.33 ± 0.23**	**2.99 ± 0.17**	**0.000***

*** P= < 0.05 is statistically significant**

Spleen size, PSR and spleen ARFI showed statistical significance between cirrhotics with EVs and cirrhotics without EVs groups.

TABLE 4: SIGNIFICANCE OF RADIOLOGICAL PREDICTORS BETWEEN LOW GRADE EVs AND HIGH GRADE EVs

PREDICTORS			
	LOW GRADE MEAN ± SD	HIGH GRADE MEAN ± SD	P value
LIVER SIZE	144.91 ± 23.39	136.74 ± 18.27	0.172
PORTAL VEIN DIAMETER	12.22 ± 2.33	12.81 ± 2.58	0.399
PV FLOW VELOCITY	18.69 ± 7.09	19.10 ± 5.52	0.819
SPLEEN SIZE	140.70 ± 31.17	153.37 ± 20.60	0.092
PLATELET SPLEEN SIZE RATIO	651.63 ± 223.87	534.75 ± 305.22	0.135
LIVER ARFI	2.99 ± 0.65	3.07 ± 0.90	0.698
SPLEEN ARFI	**3.22 ± 0.36**	**3.42 ± 0.28**	**0.001***

*** P= < 0.05 IS STATISTICALLY SIGNIFICANT**

www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858

Spleen ARFI solely independently shows statistical significance between low grade EVs and high grade EVs subgroups.

TABLE 5: ROC ANALYSIS: SPLEEN ARFI IN EVs DETECTION

PREDICTOR	CUT OFF	AUROC	SENSITIVITY	SPECIFICITY
SPLEEN ARFI	≥ 3.16	0.906	94%	92%

ROC analysis of spleen ARFI (Figure 3) in detecting EVs in this study showed maximum area under the curve of 0.906 at a cutoff of ≥ 3.16 with maximum sensitivity of 94% and specificity of 92%.

TABLE 6: ROC ANALYSIS: SPLENIC ARFI IN HIGH GRADE AND LOW GRADE EVs

PREDICTOR	CUT OFF	AUROC	SENSITIVITY	SPECIFICITY
SPLEEN ARFI	≥ 3.29	0.874	85%	100%

ROC analysis of spleen ARFI (Figure 4) in delineating high grade and low grade EVs depicted a cutoff of ≥ 3.29 with maximum area under the curve of 0.874 at cutoff of with sensitivity of 85% and specificity of 100%.

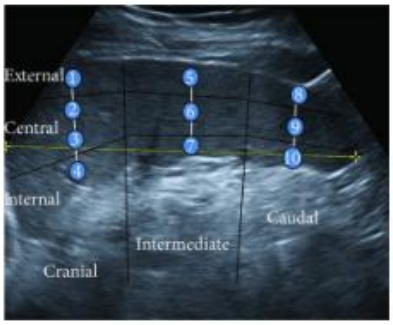

Figure: 1. Stratified random sampling method. Spleen will be subdivided into cranial external(1), cranial central(2), cranial internal(1), intermediate external(1), intermediate central(1), intermediate internal(1), caudal external(1), caudal central(1) and caudal internal (1) segments. Numbers in the parenthesis represents the number of ARFI values obtained in each segment.

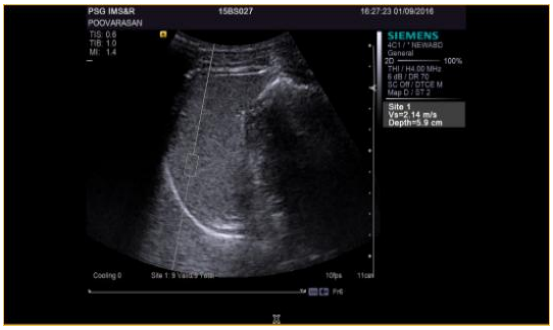

Figure: 2. In breath hold position, region of interest measuring 10mm in depth and 5mm in width was placed in parenchyma devoid of visible blood vessels and >1 cm below the level of spleen capsule and ARFI evaluation was done.

www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858

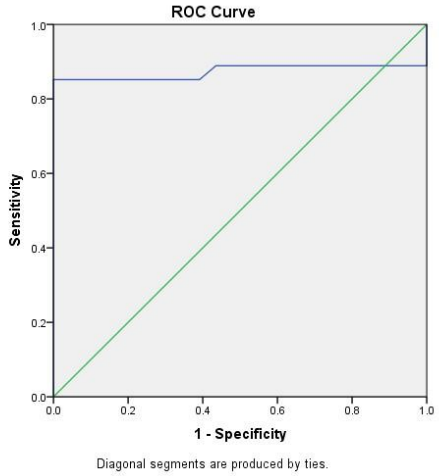

Figure: 3. ROC analysis of spleen ARFI in detecting EVs showed maximum area under the curve of 0.906 at a cutoff of ≥ 3.16 with maximum sensitivity of 94% and specificity of 92%.

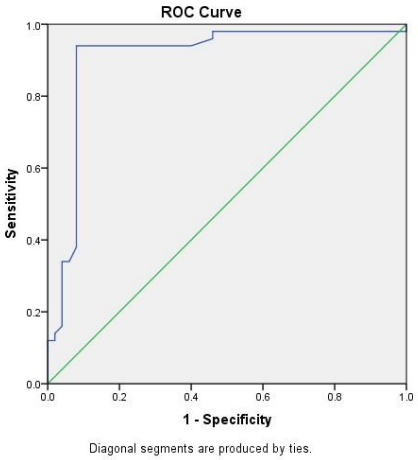

Figure: 4. ROC analysis of spleen ARFI in delineating high grade and low grade EVs depicted a cutoff of ≥ 3.29 with maximum area under the curve of 0.874 at cutoff of with sensitivity of 85% and specificity of 100%

Discussion:

Recent guidelines endorse that endoscopic screening should be done for all cirrhotic patients at the time of diagnosis to recognize those at high risk of bleeding and possibly to benefit from primary prophylaxis [6]. Implementation of these guidelines imposes huge burden on UGI scopy units and frequent testing over time can decrease the compliance of patient. By noninvasive prediction of the presence of EVs, one can recommend the appropriate category of patients to undergo invasive UGI scopy, thereby reducing unnecessary endoscopic examinations and burden on endoscopy units.

Previous studies have correlated various radiological and laboratory parameters either alone or in combination with the presence or absence of EVs in cirrhotics. Although, the efficiency of parameters or combination of parameters reported in each study differ amongst them, due to the heterogeneous nature of the studies. Good predictive value of several non-endoscopic variables for the presence or absence of EVs have been documented

www.ijbamr.com P ISSN: 2250-284X , E ISSN : 2250-2858

by many previous studies, but the data is limited from our part of the country. This study was performed to assess the effectiveness of various clinical, laboratory and radiological parameters, in reliably detecting the existence of EVs and high grade EVs in cirrhotic patients.

In the present study, there is no significant association of demographic parameters between the two study groups. Previous studies by Zaman et al [8] and Cherian et al [9], showed that Child Pugh class B or C cirrhotic patients, as compared to class A cirrhotics, have high propensity towards the detection of EVs on UGI scopy. In contrary, our study inferred no significant association between Child Pugh class and the presence of EVs (p = 0.799). In addition, we assessed MELD scores and found significant affiliation with presence of EVs, in congruence to the results of previous studies by De Mattos et al [10] , Tafarel et al [11] and Chandail VS et al [12].

Our study showed no significant variation in either portal vein diameter or portal vein flow velocity between cirrhotic patients with EVs and without EVs. Our study in contradiction to previous studies inferred that there is no significant difference in liver stiffness measured by elastography between cirrhotics with EVs and cirrhotics without EVs (p= 0.458).

In agreement with previous studies, our study also showed significant difference in the values of spleen stiffness measured by ARFI between cirrhotics with EVs and without EVs (p= 0.000). We acquired the optimal cutoff of ≥ 3.16m/s (AUROC: 0.906) with sensitivity of 94% and specificity of 92%, thereby validating spleen ARFI as a non-invasive radiological marker for the presence of EVs in cirrhotics.

In the present study, we furthermore evaluated the utility of the above discussed noninvasive clinical, laboratory and radiological parameters in the detection of high grade EVs in cirrhotics. Of all the noninvasive parameters analyzed, spleen ARFI exclusively showed significant difference between the two subgroups (p= 0.001). We derived the optimal cutoff of ≥ 3.29m/s (AUROC: 0.874) with sensitivity of 85% and specificity of 100%, which is in very close approximation with spleen ARFI cutoff of ≥ 3.30m/s obtained by Takuma et al[13]. Thereby substantiating spleen ARFI as a non-invasive radiological marker for the presence of high grade EVs in cirrhotics. In other words, the presence of high grade EVs can be reliably ruled out with the spleen ARFI cutoff of < 3.29m/s in patients with chronic liver parenchymal disease. Our study was limited by only few patients with grade IV EVs being included in this study. It is due to the lower prevalence of grade IV EVs, as in part by the practice of generous prophylactic and therapeutic measures which delays or eliminates progression of low grade EVs to high grade EVs. Inter observer variability is not assessed in this study. Future studies on this context should focus on multicenter design with evaluation of equipment of various manufacturers and assessment of inter observer variability.

Conclusions:

Amongst the noninvasive parameters analyzed in this study, spleenic ARFI exclusively showed highest sensitivity and specificity in the detection of varices and differentiation of high grade varices from low grade varices.

References :

1. Sangster GP, Previgliano CH, Nader M, Chwoschtschinsky E, and Heldmann MG. MDCT Imaging Findings of Liver Cirrhosis: Spectrum of Hepatic and Extrahepatic Abdominal Complications. HPB Surg 2013;129396:1-12.

2. Schuppan D, Afdhal NH. Liver Cirrhosis. Lancet 2008;371(9615):838-851.

3. Singh SP, Panigrahi MK. Spectrum of Upper Gastrointestinal Hemorrhage in Coastal Odisha. Trop Gastroenterol

2013;34(1):14-17.

4. Riley S, Alderson SD, Birmingham. Complications of upper gastrointestinal endoscopy. BSG Guidelines in Gastroenterology 2006 Nov:7-13.

5. Taljanovic MS, Gimber LH, Becker GW, Latt LD, Klauser AS, Melville DM et al. Shear-Wave Elastography: Basic Physics and Musculoskeletal Applications. Radiographics 2017 May-Jun;37(3):855-870.

6. Kim HY, Jin EH, Kim W, Lee JY, Woo H , Oh S et al. The Role of Spleen Stiffness in Determining the Severity and Bleeding Risk of Esophageal Varices in Cirrhotic Patients. Medicine (Baltimore) 2015 Jun;94(24):e1031.

7. Rizzo L, Attanasio M, Pinzone MR et al. A New Sampling Method for Spleen Stiffness Measurement Based on Quantitative Acoustic Radiation Force Impulse Elastography for Noninvasive Assessment of EsophagealVarices in Newly Diagnosed HCV-Related Cirrhosis. BioMed Research International 2014;Article ID 365982:1-8.

8. Zaman A, Hapke R, Flora K, Rosen HR, Benner K. Factors predicting the presence of esophageal or gastric varices in patients with advanced liverdisease. Am J Gastroenterol 1999 Nov;94(11):3292-3296

9. Cherian JV, Deepak N, Ponnusamy RP, Somasundaram A, Jayanthi V. Non-invasive predictors of esophageal varices. Saudi J Gastroenterol 2011 Jan-Feb;17(1):64-8.

10. de Mattos AZ, de Mattos AA, Daros LF, Musskopf MI. Aspartate aminotransferase-to-platelet ratio index (APRI) for the non-invasive prediction of esophageal varices. Ann Hepatol 2013 Sep-Oct;12:910-4.

11. Tafarel JR, Tolentino LH, Correa LM, Bonilha DR, Piauilino P, Martins FP et al. Prediction of esophageal varices in hepatic cirrhosis by noninvasive markers. Eur J Gastroenterol Hepatol 2011;23:754-58.

12. Chandail VS, Kotwal SK, Koul S, Gupta R, Mahajan A. Non-invasive markers for prediction of varices in patients with portal hypertension. Int J Res Med Sci 2017;5:1007-10.

13. Takuma Y, Nouso K, Morimoto Y, Tomokuni J, Sahara A, Toshikuni N et al. Measurement of spleen stiffness by acoustic radiation force impulse imaging identifies cirrhotic patients with esophageal varices. Gastroenterology 2013 Jan;144(1):92-101.