

Spleen Stiffness: A Determinant of Portal Hypertension with Esophageal Varices

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Abstract

Background:

Liver and spleen play a vital role in the splanchnic circulation. Variety of etiological agents can cause irreversible injury to hepatic cells leading to fibrosis & ultimately cirrhosis which is manifested in form of clinically significant portal hypertension and its complications including formation of varices at lower end of esophagus. Esophageal varices, an important cause of morbidity & mortality in cirrhotic patients can be diagnosed by upper gastrointestinal endoscopy and are managed according to various parameters. Recently, there is a growing interest in utilizing spleen stiffness by sonoelastography to predict portal hypertension & its complication viz. esophageal varices. Our study aimed to determine the association of splenic stiffness with portal hypertension and esophageal varices.

Materials and Methods: Sixty patients of portal hypertension, diagnosed clinically, radiologically and biochemically and those who were candidates for upper gastrointestinal endoscopy were evaluated by sonoelastography using Acoustic Radiation Forced Impulse technique to obtain mean value of spleen stiffness prior to endoscopy following IEC approval and written informed consent. The spleen stiffness measurements were then correlated with findings of endoscopy to calculate the cut-off values and various statistical parameters. In addition, spleen stiffness values were also measured in normal subjects who served as controls.

Results: Spleen stiffness was significantly higher in patients of portal hypertension than in normal subjects (3.53±0.40m/s vs 2.24±0.29m/s). Furthermore, it was higher in patients of portal hypertension with esophageal varices than those without them (3.57m/s vs 3.18m/s). Mean SS value of >2.53m/s for predicting portal hypertension yielded the sensitivity, specificity and accuracy, 98.3%, 86.7%, and 92.5% respectively while mean SS value of >3.15m/s for predicting PHTN with EV, yielded the sensitivity, specificity, and accuracy, 87%, 66.7%, and 85% respectively.

Conclusions: Mean spleen stiffness values were higher in patients with clinically significant portal hypertension than normal subjects with further higher values seen in patients of portal hypertension with esophageal varices. Hence, spleen stiffness measurement can be used as a non-invasive imaging tool for screening patients with portal hypertension as well as those with portal hypertension and esophageal varices.

Keywords: Spleen, stiffness, portal hypertension, esophageal varices

Introduction

Liver, the largest organ of the human body forms an integral part of portal venous system along with spleen. The blood

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from small and large intestines reaches the liver through the superior and inferior mesenteric, splenic, and portal veins. In normal individuals, portal venous system has a pressure of less 10mm Hg or less than 14cm of water [1].

Multiple etiological agents including alcohol, drugs and viruses may cause irreversible and irreparable damage to hepatic cells leading to fibrosis leading to increased resistance to blood flow in the hepatic sinusoids. This increased resistance may be transferred to portal vein (PV)

through backpressure changes in the portal vein radicles, segmental and lobar hepatic branches and is termed as portal hypertension (PHTN).

Clinically, the PHTN is defined as a triad of splenomegaly, dilated portal vein and presence of peritoneal fluid. Splenomegaly in PHTN is secondary to venous engorgement, tissue hyperplasia and splenic parenchymal fibrosis [2]. This fibrosis makes the splenic tissue hard and stiff.

Also, when the PHTN reaches a critical level, multiple portosystemic venous collateral channels (PSVC) open to decompress the portal venous system especially those located at lower end of esophagus and rectum, around the umbilicus, in lienorenal region and gastroepiploic ligament.

Among these the PSVC located within the mucosa of lower end of esophagus and rectum are associated with significant morbidity in the form of hematemesis and hematochezia/melena, respectively [1]. Though hematochezia/melena are commonly associated with anemia, yet mortality risk is low when compared to hematemesis due to risk of aspiration with the latter.

Chronic liver diseases (CLD) cause cirrhosis and subsequent PHTN, as its major sequelae & complications. Clinically significant PHTN is the main cause of decompensation in cirrhotic patient affecting their overall survival [3]. PHTN is a major cause of formation of esophageal varices and a direct cause of variceal hemorrhage [1]. Gastroesophageal varices are a common complication of cirrhosis and are seen in nearly half of such patients [4].

Thus, to prevent morbidity related to cirrhosis and PHTN along with their complications, it becomes imperative to identify cirrhosis before its development at the stage of hepatic fibrosis. Evaluation of liver fibrosis can be best achieved by liver biopsy which is an invasive procedure but non-invasively by sonoelastography. Recently assessment of splenic stiffness (SS) has been shown to differentiate early from late stage of hepatic fibrosis by Cabasso P, et al., as spleen plays an important role in splanchnic circulation during the development of cirrhosis with subsequent PHTN [5].

Study performed by Bota S, et al. concluded that SS by acoustic radiation forced impulse (ARFI) is a very good predictor of cirrhosis [6]. The stiffness of spleen has a mean value of approximately 2.44 m/s [7].

Esophageal varix with its risk of undergoing hemorrhage are serious and most lethal complications of cirrhosis [4]. It has been described as a medical emergency with a 6-week mortality rate of nearly 10-20% in case of bleeding [8,9]. Although an invasive procedure yet upper GI

endoscopy is still the gold standard for esophageal varices (EV) detection. Besides being invasive, UGIE is also limited by its expensive & time-consuming nature together with its lack of optimal tolerability by patients especially in a developing country like India [3]. Hence, many recent studies have focused on non-invasive prediction of hepatic fibrosis or cirrhosis & PHTN with EV by quantifying SS [10,11].

Few studies have been published in the English medical literature attempting to correlate SS measured by ARFI and PHTN with esophageal varices. Few of these studies conclude that sonoelastography using transient or ARFI methods are able to predict the clinically significant PHTN with EV [11,12]. However, fewer older studies like that published Bota S, et al. did not reveal a similar role of SS. [13] The existing dilemma on the above condition motivated us to conduct this study.

Aim

To determine the association of spleen stiffness (SS) and portal hypertension [PHTN].

Objectives

To evaluate role of spleen stiffness (SS) in predicting portal hypertension (PHTN) and esophageal varices as well as to generate cut-off values.

Materials and Methods

This hospital-based, observational, case-control study was performed on sixty patients in the Department of Radiodiagnosis of our institution over a period of 18 months following approval of Institutional Ethics Committee using strict inclusion criteria and after an informed written consent. Equal number of controls were also included in the study.

Inclusion Criteria

All patients with Portal Hypertension (PHTN) irrespective of age and sex with clinical indication of UGIE. The diagnosis of PHTN was based on history, clinical examination, laboratory, and prior radiological findings.

Exclusion Criteria

- 1) Patients undergoing or had undergone, medical/surgical treatment for PHTN.
- 2) Non-cooperative patients
- 3) Pregnancy
- 4) Gross ascites
- 5) Morbid obesity

Besides the demographic data, all the patients underwent B-

mode and SS measurements that were recorded in the predesigned patient proforma. It was followed by endoscopic evaluation for esophageal varices.

Control

Healthy subjects who gave consent for participation in the study.

Sonoelastography

Splenic stiffness (SS) by ultrasonographic examination was performed using a Siemens Acuson S2000™ ultrasound scanner with an Acoustic Forced Radiation Impulse (ARFI) enabled 6C1 curvilinear array transducer equipped with Virtual Touch Tissue Quantification (VTTQ) software. SS was measured in the right lateral decubitus posture at a depth of 2-3cm underneath the splenic capsule and expressed as shear wave velocity (meters per second, m/s). For each patient, five successful measurements were taken in mid-polar and inferior polar parenchyma during quiet breathing. The arithmetic mean value of the measurements represented the final SS value for correlation with endoscopic findings. The same procedure was adopted for control subjects also. All included patients underwent UGIE. The presence or absence of the EV was noted.

The diagnostic utility of SS by sonoelastography for identifying PHTN with and without esophageal varices was measured using appropriate statistical tools and parameters.

Observations, Results and Analysis

Age and Gender - Distribution

In our study, the median age was of patient population was 47 years while mean age was 47.2 years with majority being males (M:F=5:1).

SS correlation with presence of PHTN and EV on Endoscopy

Table 1 showed the distribution of PHTN patients with presence and absence of EV on endoscopy and mean SS in m/s. From this table, it was evident that mean SS was higher in patients with PHTN having EV and this was statistically significant

Table 1 shows distribution of SS with number of EV in our study population

| EV | Mean±SD of SS | No. of Patients |
|---------|---------------|-----------------|
| Absent | 3.18± 0.41 | 6 |
| Present | 3.57± 0.38 | 54 |
| Total | | 60 |

p= 0.024

The mean SS in control group was 2.24±0.29m/s. No significant difference was noted in mean SS values with respect to different age-groups. The mean SS value in males was slightly higher than female i.e. 2.31±0.30m/s vs 2.15±0.25m/s and this difference is found to be statistically significant with a *p*-value of 0.038.

In our study, the mean SS in control subjects was markedly lower than mean SS value in PHTN group i.e. 2.24±0.29m/s vs 3.53±0.40m/s with a *p*-value of <0.0001.

Using a balanced cut-off mean SS value of >2.53m/s for predicting portal hypertension, our study yielded the sensitivity, specificity, PPV, NPV and accuracy, 98.3%, 86.7%, 88.1%, 98.1% and 92.5% respectively.



Image 1: Shows SS value of 2.05 m/s in a control subject



Image 2: Shows SS value in patient of PHTN with no EV. The SS value is higher than that in control subject.



Image 3: Shows SS value in patient of PHTN with EV (higher than that with no EV).

Discussion

Multiple observations of our study were significant and many of them matched with the recent previous studies published in the literature while some of them were different. In the following discussion, we are comparing our observations with those made by previous researchers.

Majority of the PHTN patients in our study group were in 31-60years age-group. This was similar to study by Fierbinteanu Braticevici C. et al. [3], where the age of the patients without varices, with small varices and with varices needing treatment had a age range of 60.16+10.61, 57.61+7.14 and 62.89+9.82years respectively. In the study by Ahmed OA. et al. [14], the age of patients was 50.57+6.45years.

Our study was dominated by males (83.3% vs 16.7% females). The gender distribution was similar to that conducted by Ahmed OA. et al. [14] with 70% males and Maheswaran V. et al. [15] with 72% males.

In our study, the patients with PHTN but with no esophageal varices revealed a mean SS value of 3.18+0.41m/s. This value is higher than those obtained in other studies [3,14-16] that revealed mean SS values of 2.79+0.41m/s, 2.66+0.81m/s, 2.99+0.17m/s and 2.7+0.3m/s respectively. Though the higher SS value among patients with PHTN without varices in our study may reflect geographical and racial differences yet it may also be attributed to significantly low number of cases with no EV.

Our study revealed a higher mean SS value in PHTN patients with EV than those without EV (3.57m/s vs 3.18m/s) with a significant p-value of 0.024. Comparison of the above findings of our study with those in recent literature has been tabulated in Table 2.

From Table 2, it is well evident that the mean SS in patients without EV in our study is much higher than that reported in recent literature probably reflecting racial/demographic differences. Endemic causes like malaria, enteric fever, tropical eosinophilia affecting the spleen may also be

responsible for this high value. However, the mean SS value in patient with EV is comparable with other studies [3,14-17].

The mean SS value noted in the control group in our study was higher than that noted in the study by Ahmed OA. et al. [14] i.e. 2.24+0.29m/s vs 1.89±0.26m/s but comparable to that found in a study by Bota S. et al. i.e. 2.04+0.28m/s [13]. However, it was lower than in a study by Stefanescu M, et al. i.e. 2.7m/s [18].

Our study found significant difference in mean SS value of normal subjects and patients with PHTN. There was no significant overlap in the mean SS value of the above two groups. Adding one standard deviation to the mean SS value in normal subjects yields a value of 2.53m/s. Using this value as cut-off, we can identify patients of portal hypertension with a sensitivity, specificity, PPV, NPV and accuracy of 98.3%, 86.7%, 88.1%, 98.1% and 92.5% respectively.

Using a balanced cut-off mean SS value of >3.15m/s for predicting PHTN with EV, our study yielded the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy, 87%, 66.7%, 95.9%, 36.4% and 85% respectively.

The results of our study were similar to that described by Rastogi R., et al. in a review article [19].

Limitations of the Study

Our study was a hospital-based and cross-sectional study.

Conclusions

- Portal hypertension is commonest in 6th decade and in males.
- Mean SS value was significantly higher in patients with portal hypertension having EV than those without EV (3.57m/s vs 3.18m/s).
- Mean SS cut-off value of >3.15m/s for differentiating patients of portal hypertension with EV than those

Table 2: Shows comparison of mean SS in patients with & without EV in various studie

| Author Name with year | Mean SS with EV in m/s | Mean SS without EV in m/s | p-value |
|---|------------------------|---------------------------|---------|
| Neha et al (2020) | 3.57 | 3.18 | 0.024 |
| Fierbinteanu - Braticevici C et al (2019) | 3.37 | 2.79 | 0.001 |
| Ahmad OA et al (2019) | 3.63 | 2.66 | 0.001 |
| Maheswaran V et al (2019) | 3.33 | 2.99 | 0.000 |
| Peagu R et al (2019) | 3.40 | 2.70 | 0.001 |
| Park J et al (2016) | 3.51 | 2.30 | 0.001 |

without had a high sensitivity, PPV and accuracy with moderate specificity.

- Mean SS value in normal subjects was significantly lower than that observed in patients with portal hypertension i.e. 2.24 ± 0.29 m/s vs 3.53 ± 0.40 m/s. The normal values were slightly higher in males than females.
- A mean SS cut-off value of >2.53 m/s for identifying patients with portal hypertension had a high sensitivity, specificity, PPV, NPV and accuracy.

Portal hypertension occurring due to variety of hepatic causes is a cause of significant morbidity and mortality, primarily due to bleeding occurring from developing esophageal varices in these patients. Upper gastrointestinal endoscopy, an invasive technique is the gold standard diagnostic tool for detecting esophageal varices. Sonoelastography of spleen being non-invasive technique can be used as a screening tool to predict not only clinically significant portal hypertension but also associated esophageal varices to time the endoscopy for their appropriate management

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