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Research Article

The Utility of Spleen Stiffness Measurement in Grading the Severity of Esophageal Varices in Cirrhotic Patients

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Abstract

Introduction: Bleeding esophageal varices is a complication of liver cirrhosis with significant morbidity/mortality. Upper gastrointestinal endoscopy for variceal screening upon diagnosis of cirrhosis is recommended, however expense and invasiveness limit its use. A reproducible, non-invasive surrogate marker to screen for varices is needed. Spleen Stiffness can predict the presence and severity of varices with high accuracy. However, local data determining cut-off values of spleen stiffness in grading varix severity is lacking.

Objectives: This study aims to determine cut-off values of spleen stiffness that correlate with esophageal varix severity.

Materials and Methods: A retrospective analytic cohort study was done, analyzing 48 liver cirrhosis patients who underwent Spleen Elastography and endoscopy to evaluate for esophageal varices. Variables that showed significant difference proceeded to post hoc analysis (Duncan). The relationships between the parameters were characterized using Spearman's correlation coefficients.

Results: Spleen Stiffness was higher in patients with varices. All groups were comparable in demographics, laboratory findings, ascites, MELD and Child Pugh Class. Variceal grades I and II were higher in malignancy; grades III and IV showed higher spleen size. Grade III varices showed significantly higher stiffness. Cut-offs for Grade I, II, III varices were 6.22, 6.90, and 10.01, respectively. A cutoff value for Grade IV varices could not be set ($p = 0.436$). A significant correlation was found for both spleen size and stiffness, but stiffness was found to be more predictive of variceal grade.

Conclusion: Spleen elastography is a cost-effective, non-invasive alternative to variceal screening and should be considered in cirrhotic patients.

Keywords: Cirrhosis; Elastography; Esophageal Varix; Portal Hypertension; Spleen Stiffness

Abbreviations

MELD: Model for End Stage Liver Disease; PH: Portal Hypertension; EV: Esophageal varices; HVPG: Hepatic Venous Portal Gradient; BEV: Bleeding Esophageal Varices; SS: Spleen Stiffness; LSM: Liver Stiffness Measurement; SSM: Spleen Stiffness Measurement; HRV: High Risk Varices; NKTI: National Kidney and Transplant Institute

Introduction

Liver cirrhosis is the final evolutive stage of any chronic liver disease and its clinical outcomes are modulated by the degree of

portal hypertension. It is estimated to be responsible for over one million deaths worldwide, affecting an estimated 2% of the global population [1]. Portal hypertension (PH) is a frequent complication of cirrhosis, contributing to the development of esophageal varices (EV) [2]. The hepatic venous portal gradient (HVPG) is the standard used to determine the degree of PH and is found to correlate with the presence of EV [3]. An HVPG >10 mmHg predicts the presence of EV, while a value >12 mmHg is predictive for variceal bleeding [4]. PH results in splenic congestion and increased spleen stiffness. It also induces architectural changes in the splenic arteries and veins and induces fibrosis [5].

Bleeding esophageal varices (BEV) is a life-threatening event with a 10 - 20% mortality with each episode [6]. Due to the high pervasiveness of varices and the significant morbidity associated with variceal hemorrhage, early recognition of clinically significant esophageal varices has been the subject of many scientific inquiries. However, in clinical practice, portal hypertension and esophageal varices are evaluated mainly thru invasive procedures requiring specialized training and specialty units, either by endoscopy or hepatic vein catheterization.

Recent guidelines by the American Association for the Study of Liver Diseases recommend that all cirrhotic patients undergo screening endoscopy at diagnosis to identify varices and those who warrant primary prophylaxis against hemorrhage [5]. However, invasive testing is potentially associated with complications, related to sedation and the procedure itself, expensive and time-consuming [7]. Additionally, only 15 - 25% of patients subject to screening endoscopy were found to have medium/large varices requiring prophylactic therapy [8]. Therefore, there is a need for a non-invasive surrogate marker for the presence and severity of esophageal varices which is simple, objective, reproducible and accurate.

Review of Related Literature

Studies have found that a strong correlation was observed between clinically significant HVPG and spleen stiffness (SS), and in cases where SS measurement (SSM) was used as a screening test for the indication of esophagogastroduodenoscopy, only one of 100 screened patients would have wrongly avoided esophagogastroduodenoscopy (EGD) [9]. In a local study done by Calimag., *et al*. [11], a total of 29 subjects underwent spleen elastography and they found a strong positive correlation of spleen stiffness and severity of esophageal varices (r = 0.821) (i.e. spleen stiffness was increased in patients with endoscopically larger varices), but a lesser degree of correlation between spleen diameter and severity of esophageal varices (r = 0.446) [11]. The same study also concluded that spleen size did not produce a significant difference in between groups of variceal size (implying that it may not be accurate in predicting and monitoring esophageal varix progression), but the lack of effect may be due to the small sample size utilized in the study [11].

The splenic changes observed in patients with portal hypertension is not simply attributed to passive spleen congestion, but also to tissue hyperplasia characterized by a combination of angiogenesis, fibrogenesis, enlargement and hyperactivation of splenic lymphoid compartment [12]. These changes may be better observed through elastography and is better reflective of complex hemodynamic changes observed in portal hypertension [3,5]. Hence, the usefulness of splenomegaly and spleen stiffness in the diagnosis of portal hypertension and prediction of esophageal varices has been a matter of recent scientific interest.

SSM can be used to predict the presence and severity of esophageal varices with high degree of accuracy in patients with chronic liver disease. In one study done on Hepatitis C- predominant patients, elastography had a sensitivity of 98.5% and specificity of 98.9%, respectively [5]. SS predicts the formation of esophageal varices caused by splanchnic hemodynamic changes better than liver stiffness. To date, only 1 local correlational study proving the utility of spleen elastography in predicting the severity of esophageal varices was done, but there is yet to be a local study that determines cut-off values of spleen stiffness in grading esophageal varix severity.

Definition of terms

1. **Spleen stiffness:** An ultrasonographic measure, expressed in kPa, reflective of portal hypertension-related changes in the spleen, including splenomegaly.
2. **Spleen diameter:** The largest dimension of the spleen determined via ultrasonography. Expressed in centimeters.
3. **Spleen point shear wave elastography:** A non-invasive method proposed for the assessment of splenic fibrosis in patients with chronic liver disease by measuring spleen stiffness via ultrasound.

4. **Portal hypertension:** A clinical condition characterized by a high blood pressure in the portal vein and its tributaries and it is defined as a gradient between portal and systemic blood pressure > 6 mmHg.
5. **MELD (Model of end-stage liver disease) score:** Used to estimate relative disease severity and prognosis of patients with chronic liver disease. It is computed using the following parameters: Creatinine, Bilirubin, INR, Dialysis at least twice in the past week.
6. **Esophageal varices grading:** A method used in this study to quantify esophageal varix severity by size as observed thru endoscopy:
    a. Grade I: Small straight esophageal varices.
    b. Grade II: Enlarged, tortuous varices occupying less than 1/3 the lumen.
    c. Grade III: Large, coil shaped esophageal varices occupying more than 1/3 of the lumen.
    d. Grade IV: Racemose varices occluding the lumen, particularly marked with cherry red spots or varices on varices ("cherry red varices").

Research Objectives

General objectives: To determine cut-off values of spleen stiffness measured by point shear wave elastography in grading esophageal varix severity.

Specific objectives:

1. To determine the demographic profile of Liver Cirrhosis patients at a tertiary referral center.
2. To determine the spleen stiffness as measured by point shear wave elastography in known cirrhotic patients at a tertiary referral center.
3. To determine the presence and severity of esophageal varices among patients with Liver Cirrhosis at a tertiary referral center.
4. To determine cut-off values of spleen stiffness that correlate with esophageal varix severity.

Research Question

What cut off value for spleen stiffness via spleen elastography may be used to grade esophageal varix severity?

Materials and Methods

Study design: A retrospective analytic cohort study.

Study setting and time period: Conducted from August 2018 to March 2020 at a tertiary referral center that caters to challenging liver patients and liver transplantation.

Study population and sample size: All Liver Cirrhosis Patients, regardless of cause, seen at NKTI from August 2018 to March 2020 were included. Both outpatients or inpatients were included in the study. Patients with previous EGD and Spleen Elastography were enrolled. A non-probability convenience sampling method was employed.

Inclusion criteria:

1. All Liver Cirrhosis Patients above 18 years old, regardless of cause of cirrhosis.
2. Patients diagnosed with liver cirrhosis made by a combination of clinical, biochemical (platelet count, international normalized ratio, prothrombin time, alanine aminotransferase [ALT], albumin, bilirubin), and radiographic imaging (Ultrasound or CT Scan; Liver size and Characteristics).
3. All patients underwent upper GI endoscopy and Spleen Elastography.

Exclusion criteria:

1. Patients who did not undergo both procedure or underwent only one of the specified procedures.
2. Presence of portal vein thrombosis on imaging.
3. Those patients who were hemodynamically unstable to undergo endoscopy.

study procedure

All study participants had a previous EGD and spleen elastography done as out/inpatient. The principal investigator conducted a chart review of the patients in the study. Diagnostics/imaging/endoscopy reports were reviewed from the inpatient chart at the medical records or outpatient chart from the attending physician's clinic. Consent for review of the chart was taken from the chief of the medical records division and attending physician.

Statistical analysis

Descriptive statistics was used to summarize the demographic

and clinical characteristics of the patients. Frequency and proportion were used for categorical variables. Mean and SD were used for normally distributed continuous variables. Chi Square test (for categorical variables) and t-test (for continuous variables) were used to determine the difference between liver cirrhotic patients with and without varices in terms of demographic and clinical characteristics of the patients. Kruskal Wallis (for categorical variables) and One way ANOVA (for continuous variables) were used to determine the difference among the different grades of esophageal varices in terms of demographic and clinical characteristics of the patients. Variables that showed significant difference were further subjected to post hoc analysis (Duncan) to determine subsets. The relationships between the parameters were characterized using Spearman's correlation coefficients. Missing variables were neither replaced nor estimated. Null hypotheses were rejected at 0.05 α-level of significance. SPSS version 17.0 was used for data analysis.

Ethical considerations

Informed consent, confidentiality and security of information

Permission and approval from the Institutional Ethics and Review Board (IERB) were obtained prior to the start of the study. Before the commencement of data collection, consent was taken from the medical records/ attending physician for review of the patient's chart.

All data gathered were kept confidential and were used only for the purposes of the study. Patients were assigned an alphanumeric code known only to the investigator. The code assigned to each patient was used to track the date and keep the patient anonymous. All personal data were kept in a secure location under lock and key. Confidential information was not shared during the publication of the research.

Results

A total of 48 patients were enrolled after the 1.6-year period. The baseline clinical, biochemical endoscopic and radiological findings of the study population are summarized in table 1.

Variable	n	Frequency (%)	Mean	±	SD
Age (years)	48		57.65	±	15.20
Sex	48				
Male		25 (52.1%)			
Female		23 (47.9%)			
Etiology	48				
Hep B		32 (66.7%)			
NAFLD		9 (18.8%)			
ALD		2 (4.2%)			
Others		5 (10.4%)			
Malignancy	48	12 (25.0%)			
Laboratory Findings					
ALT (IU/L)	47		56.66	±	54.38
AST (IU/L)	40		96.68	±	114.49
Albumin (g/dL)	37		3.22	±	0.73
Bilirubin (mg/dL)	46		4.98	±	8.21
Platelet Count (x10^3/uL)	48		145.73	±	86.81
INR	46		1.32	±	0.31
Creatinine (mg/dL)	48		1.14	±	1.45
Na (mmol/L)	47		136.94	±	6.41
Radiologic Findings					
Spleen Size	48		513.96	±	551.25
Spleen Diameter (cm)	48		12.49	±	3.28
Ascites on Imaging	45				
None		21 (46.7%)			
Minimal		11 (24.4%)			
Moderate		9 (20.0%)			
Massive		4 (8.9%)			
Esophageal Varices	48				
No Varices		14 (29.2%)			
Grade I		10 (20.8%)			
Grade II		10 (20.8%)			
Grade III		`8 (16.7%)			
Grade IV		6 (12.5%)			
MELD Score	46		15.24	±	7.76
Child Pugh Score	18		8.39	±	2.28
Spleen Stiffness (kPa)	48		11.69	±	7.61

Table 1: Baseline characteristics of study population with liver cirrhosis.

Of 48 patients, majority were male (n = 25, 52.1%). The primary etiologies of the underlying chronic liver disease were Viral Hepatitis B (n = 32, 66.7%), Non-Alcoholic Fatty-liver Disease (n = 9, 18.8%), Alcoholic Liver Disease (n = 2, 4.2%) and Others comprised as: AIH (n = 1, 2.1%), Cardiac Cirrhosis (n = 1, 2.1%), Schistosomiasis (n = 1, 2.1%), Hepatitis C (n = 1, 2.1%) and Cryptogenic (n = 1, 2.1%). 25% of patients had hepatocellular carcinoma (n = 12). The mean Spleen diameter was 12.49 ± 3.28 cm and Spleen stiffness was 11.69 ± 7.61 kPa. The mean MELD Score was 15.24 ± 7.76. The mean Child Pugh Score was 8.39 ± 2.28. Majority had no ascites on imaging (n = 21, 46.7%). Endoscopic examination revealed varices in 34 patients (71%) with variceal grade 1, grade 2, grade 3 and grade 4 found in 10 (20.8%), 10 (20.8%), 8 (16.7%) and 6 (12.5%), respectively. No varices were seen in 14 patients (29.2%).

Table 2 provides a summary comparison of clinical characteristics between cirrhotic patients with varices and without varices. No significant difference was observed in age, sex, etiology of cirrhosis, presence of malignancy, laboratory/radiologic findings, MELD score and Child Pugh Score between patients with and without esophageal varices. Spleen Stiffness was significantly higher in patients with esophageal varices compared to those without varices (p = 0.014).

Variable	Without Varices (n=14)				With Varices (n=34)				p-value
	Frequency (%)	Mean	±	SD	Frequency (%)	Mean	±	SD	
Age (years)		61.50	±	12.11		56.06	±	16.20	0.264
Sex									0.145
Male	5 (35.7%)				20 (58.8%)				
Female	9 (64.3%)				14 (41. 2%)				
Etiology									0.760
Hep B	10 (71.4%)				22 (64.7%)				
NAFLD	3 (21.4%)				6 (17.6%)				
ALD	0 (0.0%)				2 (5.9%)				
Others	1 (7.1%)				4 (11.8%)				
Malignancy	2 (14.3%)				10 (29.4%)				0.271
Laboratory Findings									
ALT (IU/L)		41.36	±	27.75		63.15	±	61.58	0.212
AST (IU/L)		67.50	±	61.64		106.40	±	126.71	0.359
Albumin (g/dL)		3.30	±	0.89		3.20	±	0.69	0.727
Bilirubin (mg/dL)		4.34	±	6.30		5.26	±	9.00	0.730
Platelet Count (x10^3/uL)		133.43	±	48.11		150.79	±	98.64	0.534
INR		1.34	±	0.37		1.31	±	0.29	0.731
Creatinine (mg/dL)		0.91	±	0.28		1.24	±	1.71	0.477
Na (mmol/L)		135.64	±	8.03		137.48	±	5.65	0.374
Radiologic Findings									
Spleen Size		320.98	±	461.86		593.43	±	571.36	0.121
Spleen Diameter (cm)		11.093	±	3.48		13.06	±	3.06	0.057
Ascites on Imaging									0.590
None	7 (53.8%)				14 (43.8%)				
Minimal	4 (30.8%)				7 (21.9%)				
Moderate	1 (7.7%)				8 (25.0%)				
Massive	1 (7.7%)				3 (9.4%)				
MELD Score		14.929	±	7.25		15.38	±	8.09	0.860
Child Pugh Score		9.00	±	3.61		8.27	±	2.09	0.626
Spleen Stiffness (kPa)		7.54	±	4.45		13.40	±	8.03	0.014*

Table 2: Comparison of clinical characteristics between cirrhotic patients with and without esophageal varices.
*: Indicates significant difference at alpha 0.05.

Table 3 summarized the clinical characteristics between cirrhotic patients according to the degree of esophageal varices. All groups were comparable in demographics, clinical profile, laboratory findings, ascites on imaging, MELD score and Child Pugh Class. There was a significant difference among the five groups in terms of malignancy (p = 0.037), spleen size (p = 0.032), and spleen stiffness (p = 0.00).

Variable	Without Varices (n=14)				Grade I (n=10)				Grade II (n=10)				Grade III (n=8)				Grade IV (n=6)				p-value
	Frequency (%)	Mean	±	SD	Frequency (%)	Mean	±	SD	Frequency (%)	Mean	±	SD	Frequency (%)	Mean	±	SD	Frequency (%)	Mean	±	SD	
Age (years)		61.50	±	12.11		60.10	±	12.40		58.90	±	18.41		49.88	±	14.87		52.83	±	20.32	0.429
Sex																					0.515
Male	5 (35.7%)				7 (70.0%)				5 (50.0%)				4 (50.0%)				4 (66.7%)				
Female	9 (64.3%)				3 (30.0%)				5 (50.0%)				4 (50.0%)				2 (33.3%)				
Etiology																					0.233
Hep B	10 (71.4%)				7 (70.0%)				8 (80.0%)				5 (62.5%)				2 (33.3%)				
NAFLD	3 (21.4%)				2 (20.0%)				2 (20.0%)				1 (12.5%)				1 (16.7%)				
ALD	0 (0.0%)				0 (0.0%)				0 (0.0%)				1 (12.5%)				1 (16.7%)				
Others	1 (7.1%)				1 (10.0%)				0 (0.0%)				1 (12.5%)				1 (16.7%)				
Malignancy	2 (14.3%)				6 (60.0%)				3 (30.0%)				0 (0.0%)				1 (16.7%)				0.037*
Laboratory Findings																					
ALT (IU/L)		41.36	±	27.75		101.20	±	92.23		50.20	±	43.08		43.29	±	25.24		44.50	±	25.56	0.061
AST (IU/L)		67.50	±	61.64		133.44	±	166.60		98.20	±	134.46		118.00	±	110.35		69.83	±	56.91	0.740
Albumin (g/dL)		3.30	±	0.89		3.51	±	0.70		3.19	±	0.73		2.86	±	0.61		3.02	±	0.66	0.540
Bilirubin (mg/dL)		4.34	±	6.30		5.43	±	10.07		3.66	±	4.58		4.69	±	6.32		8.36	±	15.40	0.858
Platelet Count (x10^3/uL)		133.43	±	48.11		155.60	±	56.14		141.40	±	96.95		109.63	±	66.63		213.33	±	166.69	0.246
INR		1.34	±	0.37		1.30	±	0.28		1.28	±	0.32		1.30	±	0.26		1.36	±	0.33	0.984
Creatinine (mg/dL)		0.91	±	0.28		1.24	±	1.19		1.61	±	2.92		0.79	±	0.23		1.22	±	0.89	0.763

Na (mmol/L)		135.64	±	8.03		138.80	±	6.36		137.60	±	3.66		139.43	±	5.19		132.83	±	6.37	0.289
Radiologic Findings																					
Spleen Size		320.98	±	461.86		352.20	±	378.25		485.93	±	417.31		1043.76	±	646.45		574.20	±	730.83	0.032*
Spleen Diameter (cm)		11.09	±	3.48		11.88	±	1.96		12.70	±	3.78		15.11	±	3.01		12.92	±	2.60	0.079
Ascites on Imaging																					0.125
None	7 (53.8%)				1 (11.1%)				6 (60.0%)				6 (75.0%)				1 (20.0%)				
Minimal	4 (30.8%)				5 (55.6%)				2 (20.0%)				0 (0.0%)				0 (0.0%)				
Moderate	1 (7.7%)				2 (22.2%)				1 (10.0%)				1 (12.5%)				4 (80.0%)				
Massive	1 (7.7%)				1 (11.1%)				1 (10.0%)				1 (12.5%)				0 (0.0%)				
MELD Score		14.93	±	7.25		16.60	±	9.12		13.22	±	5.56		13.57	±	7.00		18.67	±	10.89	0.675
Child Pugh Score		9.00	±	3.61		7.33	±	1.63		9.00	±	2.83		10.00	±	0.00		8.67	±	2.42	0.742
Spleen Stiffness (kPa)		7.54	±	4.45		8.33	±	3.93		10.85	±	4.70		23.13	±	8.61		13.13	±	6.17	0.000**

Table 3: Comparison of clinical characteristics between cirrhotic patients.
*: Indicates significant difference at alpha 0.05, **: At alpha 0.01.

Post hoc analysis (Duncan) revealed the following: first, variceal grades I and II were found to be significantly higher in malignancy compared to other grades; second, variceal grades III and IV showed higher spleen size compared to other groups; lastly; a highly significant difference was found between variceal grades, such that grade III varices showed significantly higher stiffness compared to other groups.

Note that the 27 of the 48 spleen sizes were reported as 3- dimensional values (cm^3), while the rest (21) were 2- dimensional (cm^2). To be able to compare them, the volume of the 3-dimensional values and the area of the 2-dimensional values were obtained. This might explain the high SD between spleen sizes. Nevertheless, a significant difference ($p = 0.032$) was found between groups.

Based on the ROC Curve (See figure 1), cut-off values for spleen stiffness and their corresponding sensitivity and specificity were derived, as shown in table 4 and figure 2. P- values were highly significant ($p < 0.01$) for cut-off values for Grade I, II and III varices; however, since the p value ($p = 0.436$) was not significant for Grade IV, a cut-off value could not be set for Grade IV varices. A kPa greater than or equal to 6.22 is 88.2% sensitive and 64.3% specific for grade I varices. A kPa greater than or equal to 6.90 is 87.5% sensitive and 54.2% specific for grade II varices. A kPa greater than or equal to 10.01 is 85.7% sensitive and 70.6% specific for grade III varices.

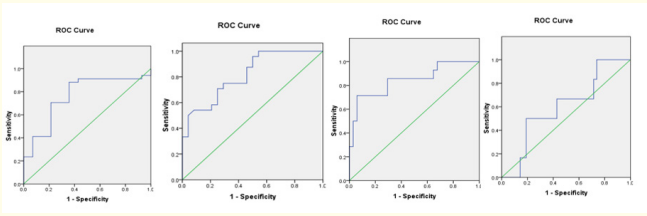

Figure 1: ROC curve for cut-off values of grade 1-4 varices (from left to right).

	kPa Cut Off Value	% Sensitivity	% Specificity	p-value
Grade I	6.22	88.2	64.3	0.005**
Grade II	6.90	87.5	54.2	0.000**
Grade III	10.01	85.7	70.6	0.000**
Grade IV	10.01	66.7	57.1	0.436

Table 4: kPa cut-off values.

*: Indicates significant difference at alpha 0.05, **: At alpha 0.01.

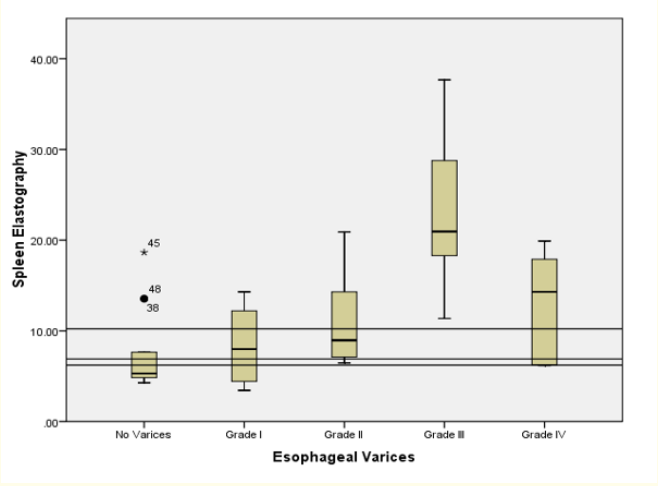

Figure 2: Box plot of kPa cut-off values.

Using Spearman's rho, a positive correlation was found between variceal severity and spleen size (r = 0.339) and variceal severity and spleen stiffness (r = 0.554) (See table 5 and figure 3 at the Appendix). As variceal grade increases, an increase in spleen size and stiffness are observed. A significant correlation was found for both spleen size (p = 0.018) and spleen stiffness (p = 0.00), but spleen stiffness was found to be more predictive of variceal grade.

Variable	r	p-value
Spleen Size	0.339	0.018*
Spleen Stiffness	0.554	0.000**

Table 5: Correlation between variceal severity and spleen size/ spleen stiffness.

*: Indicates significant difference at alpha 0.05, **: At alpha 0.01.

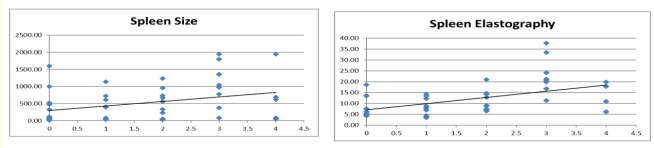

Figure 3: Scatter plot of spleen size/stiffness distribution per variceal grade with best fit line showing correlation.

Discussion

The outcomes of this study showed that patients with esophageal varices had higher spleen stiffness compared to those patients without varices. In comparison to liver stiffness measurement (LSM) which may be influenced by inflammation, congestion, obstructive jaundice and hepatic blood flow influence which could all simulate "fibrosis" and overestimate values, SS seems able to overcome these factors, making it a more objective marker regardless of the cause [13]. Increased intrasplenic pressure from PH makes it a more accurate predictor of portal pressure [13].

Logically, the higher the esophageal grade, the greater the spleen stiffness (kPa). This was evident in this study where an increasing trend of mean spleen size, diameter and stiffness were observed as the variceal severity increased from None up to Grade III. However, due to the under-representation of patients with grade IV varices (6 of 48) and the small sample size utilized in the study, the relatively low mean values for grade 4 was not consistent with

this upward trend. A similar study by Kim., *et al*. also found that SS measured by elastography was effective in detecting varices and in predicting the presence of high risk varices [5].

In this study, a higher spleen size did not seem to equate to higher spleen diameter. This might be due to the high SD values between spleen sizes as 27 of 48 values were reported as 3-dimension (cm^3) and 21 of 48 as 2-dimension (cm^2); even then, a positive correlation was significant between variceal grade and spleen size.

This study was also able to determine cut-off values that could correlate with esophageal varix severity. However, owing to the small number of cirrhotic patients with Grade 4 varices, a precise cut-off for this grade could not be determined. To date, no recent literature also tried to determined cut-off values for variceal grade severity based on SSM.

Recent literatures cited the Baveno VI guideline to spare screening endoscopies in patients with LSM < 20 kPa and platelet count > 150 G/L and rule out high risk varices (HRV) needing treatment [14]. A study done by Colecchia., *et al*. found that by using SSM as a single diagnostic test to rule out HRV with a single cut-off ≤ 46 kPa, the proportion of avoided endoscopies was 35.8%, significantly ($p < 0.01$) higher than obtained by applying the Baveno VI criteria (21.7%) [15]. Another study by Stefanescu., *et al*. combined LSM (cutoff: 19 kPa) and SSM (cutoff: 55kPa) into a simple diagnostic algorithm to rule-in any EV with a sensitivity of 93% and a PPV of 95% [10]. The higher cut-off values for SS in the above studies may be due to higher spleen length and volume and height and weight of Caucasians compared to their Asian counterparts [16].

This study also found that lower variceal grades (I and II) were significantly higher in malignancy. Though EV were thought to be more prevalent in advanced Child Pugh Class and hepatocellular cancer (HCCA), making it a marker of poorer prognosis, Giannini., *et al*'s study showed that 56% of the HCCA patients presented with well-compensated cirrhosis, whereby most varices were small in 352 patients (48.2% of the EV population) and medium in 220 patients (30.1%) with HCCA [17]. Whether other factors such as structural/nutritional factors in the HCCA patient contribute to lower variceal grade is uncertain. No other available literature correlated malignancy with variceal grade.

Xing Hu., *et al*. [18] in their meta-analysis indicated that spleen stiffness measured by current techniques had a fairly good accuracy for the detection of PH and EV in CLD patients. In their article, the AUCs for diagnosis of any EV and HREV reached 87% and 83%, respectively. The results of our study is relatively comparable to this. Furthermore, Xing Hu., *et al*. observed that the diagnostic performance of SSM for detecting any EV was better across Asian populations than in European populations. This is because prior studies have shown that BMI and central obesity are independent influencing factors for the failure and unreliability of ultrasound in measuring spleen stiffness. The mean BMI of European subjects in other studies was obviously higher than that of Asian subjects. Majority of the patient subjects in our study belonged to the normal BMI range, hence, spleen elastography was performed without too much difficulty.

The limitations of the current study include the small sample size with a mostly homogenous etiologic cause of liver cirrhosis. A larger sample size with wider variety of cirrhosis etiology may produce different results, as SS may be different for esophageal varix prediction amongst different causes of portal hypertension[8]. The cut-off values and findings above are only representative of and/or applicable to the cirrhotic population studied in NKTI.

Conclusion

In conclusion, the results of this study provide insight into the diagnostic potential of SS in the screening and grading of esophageal varices in patients with liver cirrhosis. SS may prove to be a reliable, non-invasive alternative to endoscopy, especially in the Philippine setting where endoscopy units are scarce and healthcare costs are high. The use of spleen elastography should be considered in patients with cirrhosis as it may help identify those with high risk varices requiring treatment and assist the physician in deciding which patients can safely avoid endoscopy.

Recommendations

Since cut-off values for Grade IV varices could not be obtained in this study due to the low sample size, a large-scale prospective study including other hospitals in the Philippines may be needed to improve generalizability of the results and cut-off values for spleen stiffness. A larger population size might also show higher diagnostic accuracy of spleen elastography and determination of cut-off value of spleen stiffness for grade IV varices.

The primary investigator recommends a follow-up study incorporating liver stiffness measurement and platelet count with

spleen stiffness measurement to come up with a prediction model applicable in the Philippine setting to rule out high risk varices.

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