ABSTRACT

Introduction: Bleeding esophageal varices is a complication of liver cirrhosis resulting from portal hypertension that carries significant morbidity, mortality and healthcare costs. There is a need for a safe, reproducible and non-invasive surrogate marker to accurately screen for esophageal varices. Spleen Stiffness can predict the presence and severity of varices in cirrhotic patients with high diagnostic accuracy. However, local data establishing the usefulness of splenic stiffness in predicting the severity of esophageal varices is lacking.

Objectives: To determine the correlation of splenic stiffness measured by transient elastography to presence and severity of esophageal varices.

Materials and Methods: An Ambispective analytic cohort study. A total of 29 patients underwent Spleen stiffness determination by Point Shear wave Elastography and Upper Gastrointestinal endoscopy to evaluate for esophageal varices. Relationships between the parameters were characterized using Spearman's correlation coefficients. One-way ANOVA and Fisher's exact test was used to determine the difference between four different grades of esophageal varices.

Results: 19 patients (65.5%) had varices with grade 1 (n=5, 17.24%), grade 2(n=7, 24.14%), and grade 3 (n=7, 24.14%) respectively. There was a significant difference among four groups in terms of spleen diameter ($p = 0.048$) and Spleen Stiffness ($p= <0.001$). A strong positive correlation of Spleen stiffness and severity of esophageal varices ($r = 0.821$) was noted. Spleen diameter and severity of esophageal varices were directly correlated but to a lesser degree ($r= 0.446$).

Conclusion: Spleen elastography appears to be a reliable, non-invasive and cost-effective method of variceal screening and should be considered in cirrhotic patients.

KEYWORDS: *Esophageal Varices; Elastography; Spleen Diameter; Transient Elastography;*

WORD COUNT: 250 Words

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[3]. Portal hypertension is a frequent complication of cirrhosis, contributing to the development of ascites, esophageal varices and hepatic encephalopathy[5]. A portal pressure gradient >10 mmHg is necessary for the development of esophageal varices, ascites and other complications.

Esophageal varices is one of the serious complications of liver cirrhosis resulting from portal hypertension. Bleeding esophageal varices is a life-threatening event with a 10-20% mortality each episode[5]. 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 warrant primary prophylaxis against hemorrhage if indicated. Nonetheless, invasive testing is potentially associated with complications, related to sedation and the procedure itself, as well as increased costs of medical care[7]. Majority of cirrhotic patients who undergo

screening endoscopy either do not have varices or have varices that are too small to warrant prophylactic therapy. 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.

In recent years, liver stiffness has shown utility in the assessment of portal hypertension and its complications. Liver stiffness measured by transient elastography may represent a rapid and noninvasive method for predicting the presence of clinically significant or severe portal hypertension. However, liver stiffness shows a poor correlation with hepatic venous pressure gradient (HVPG) values greater than 12 mmHg because of the increasing relevance of extrahepatic factors contributing to the progression of PH.[3] Thus, it is not an adequate predictor for the presence and grade of esophageal varices. Liver stiffness only reflects the increased intra-hepatic vascular resistance but not the hyperdynamic circulation and opening of the portal systemic shunts[8]. A meta-analysis done by Dujunco et. Al (2017)[4] in the Philippines concluded that Liver stiffness, spleen diameter and Platelet ratio score cannot replace gastroscopy to determine the presence of Esophageal varices. Hence a more sensitive non-invasive test is needed to determine the need to undergo gastroscopy for esophageal varices among cirrhotic patients.

Splenomegaly is a common finding in patient with cirrhotic patients and is due to blood congestion, increased portal pressure, augmented resistance to splenic vein outflow and increased angiogenesis and fibrogenesis. All these changes result in increased splenic stiffness which is closely related to portal hypertension and reflects the extrahepatic hemodynamic changes.[5] Hence, the

usefulness of splenomegaly and spleen stiffness in the diagnosis of portal hypertension has been studied.

Portal hypertension-related changes in the spleen can be seen by transient elastography and has been used to predict both the presence of portal hypertension as well as esophageal varices. Spleen stiffness measurement can be used to predict the presence and severity of esophageal varices with high degree of accuracy in patients with chronic liver disease. Splenic stiffness using elastography was effective in detecting varices and predicting presence of high risk varices in Hepatitis C predominant patients with a sensitivity of 98.5% and 98.9%, respectively.[5] Spleen stiffness predicts the formation of esophageal varices caused by splanchic hemodynamic changes better than liver stiffness. To date, there is no local study established in our setting that investigates the usefulness of splenic stiffness in predicting the presence and severity of esophageal varices. If proven, splenic stiffness determination by transient elastography may be used as a noninvasive, affordable and safe alternative diagnostic method to screen for esophageal varices.

DEFINITION OF TERMS

1. **Splenic 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. **Splenic Transient 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 1: small straight esophageal varices
    b. Grade 2: Enlarged, tortuous varices occupying less than 1/3 the lumen.
    c. Grade 3: large, coil shaped esophageal varices occupying more than 1/3 of the lumen

RESEARCH OBJECTIVES

1. **General Objectives:** To determine the correlation between Splenic stiffness measured by transient elastography and the presence and severity of esophageal varices among known cirrhotic patients.
2. **Specific Objectives**:
    a) To determine the demographic profile of Liver Cirrhosis patients at a tertiary referral center

b) To determine the splenic stiffness as measured by transient elastography in known cirrhotic patients at a tertiary referral center
c) To determine the presence and severity of esophageal varices among patients with Liver Cirrhosis at a tertiary referral center
d) To compare spleen stiffness and spleen diameter in detecting varices

RESEARCH QUESTION

Is there a correlation between splenic stiffness, presence and severity of esophageal varices in cirrhotic patients?

RESEARCH HYPOTHESIS

1. **NULL HYPOTHESIS:** There is no correlation between splenic stiffness, presence, and severity of esophageal varices in cirrhotic patients.
2. **ALTERNATIVE HYPOTHESIS:** There is a correlation between splenic stiffness, presence and severity of esophageal varices in cirrhotic patients.

MATERIALS AND METHODS

1. **STUDY DESIGN:** An Ambispective (combined Retrospective and Prospective) analytic cohort study
2. **STUDY SETTING AND TIME PERIOD:** Conducted from August 2018 to November 2018 at a tertiary referral center that caters to challenging liver patients and liver transplantation.
3. **STUDY POPULATION AND SAMPLE SIZE**: All Liver Cirrhosis Patients, regardless of cause, seen at NKTI from August 2018 to November 2018

were included. Both outpatients or inpatients were included in the study. Patients with previous EGD and Spleen Elastography were also enrolled. A non-probabilistic convenience sampling method was employed. A sample size of 29 was computed to achieve 81% power and to detect a difference of -0.50000 between the null hypothesis correlation of 0.00000 and the alternative hypothesis correlation of 0.50000 using a two-sided hypothesis test with a significance level of 0.05000.

A. INCLUSION CRITERIA:

I. All Liver Cirrhosis Patients above 18 years old, regardless of cause of cirrhosis.

II. Patients diagnoses 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).

III. All patients underwent upper GI endoscopy and Splenic Elastography.

B. EXCLUSION CRITERIA:

I. Patients who were not willing to undergo both procedure or will undergo only one of the specified procedures.

II. Presence of Portal Vein thrombosis on imaging

4. PATIENT RECRUITMENT

Patients were invited to participate in the study from the outpatient department or Inpatient during admission. Some patients were recruited for

the study prior to any of the proposed procedure or after Upper GI endoscopy has been done. Some patients with both Upper GI endoscopy and Spleen Elastography already done were also included. Consent was secured either by the principal investigator with the permission of the attending physician or by the Co-investigators.

5. STUDY PROCEDURE

SPLENIC STIFFNESS MEASUREMENT: All spleen stiffness measurement was done by an experienced senior radiologist using Phillips iU22 Ultrasound System. Point Shear wave Elastography was done for 15 repetitions in the spleen on all patients. Same basic procedure for scanning for splenic stiffness was done to all eligible patients. There were no reported adverse events noted with spleen stiffness measurement. Results were expressed in Kpa.

UPPER GI ENDOSCOPY: All eligible patients underwent upper endoscopy as part of standard of care in compliance to current recommendations of American Association for the Study of Liver Diseases. No adverse events were reported during the study period. All Upper GI endoscopies were done by experienced GI endoscopists. All Esophageal varices were graded 1-3. (1: small straight esophageal varices; 2: Enlarged, tortuous varices occupying less than 1/3 the lumen. 3: large, coil shaped esophageal varices occupying more than 1/3 of the lumen).

STATISTICAL ANALYSIS

Descriptive statistics was used to summarize the demographic and clinical characteristics of the patients. Frequency and proportion was used for categorical variables. Mean and SD were used for normally distributed continuous variables. One-way analysis of variance and Fisher's exact test was used to determine the difference between four different grades of esophageal varices in terms of demographic and clinical characteristics of the patients. The relationships between the parameters were characterized using Spearman's correlation coefficients. Missing variables were neither replaced nor estimated. Null hypotheses were rejected at 0.05α-level of significance. STATA 13.1 was used for data analysis.

RESULTS

A total of 29 patients were enrolled after the 90 day period. The baseline clinical, biochemical endoscopic and radiological findings of the study population are summarized in Table 1.

Table 1. Baseline Characteristics of Study Population with Liver Cirrhosis (n = 29)

Variable	Frequency (%); Mean ± SD;
Age	57.62 ± 13.67
Sex	
Male	16 (55.17)
Female	13 (44.82)
Etiology	
HBV	16 (55.17)
NAFLD	5 (17.24)
Alcoholic	0
Others	8 (27.58)
With malignancy	6 (20.6)
Laboratory findings	
ALT	51.41 ± 39.59
Bilirubin	5.07 ± 7.29
Platelet count	137.52 ± 74.6
INR	1.32 ± 0.32
Creatinine	0.90 ± 0.72
Na	136.41 ± 6.36
Esophageal Varices	
No Varices	10 (34.48)
Grade 1	5 (17.24)
Grade 2	7 (24.14)
Grade 3	7 (24.14)
Spleen diameter	12.37 ± 3.39
MELD score	15.24 ± 7.77
Spleen Stiffness	11.77 ± 8.87

Of 29 patients, majority were male (n=16, 55.17%). The primary etiologies of the underlying chronic liver disease were viral hep B (n=16, 55.17%), Non-Alcoholic Fatty-liver Disease (n=5, 17.24%), Cardiac Cirrhosis (n=1, 3.4%), Schistosomiasis (n=1, 3.4%) and Cryptogenic (n=1, 3.4%). 6 patients had primary intrahepatic malignancy (n=6, 20.6%). The mean Spleen

diameter and Spleen stiffness were 12.37 ± 3.39 and 11.77 ± 8.87, respectively. The mean MELD Score was 15.24 ± 7.77. Endoscopic examination revealed varices in 19 patients (n=19, 65.5%) with variceal grade 1, grade 2, and grade 3 found in 5 (17.24%), 7 (24.14%) and 7 (24.14%) respectively. No Varices were seen in 10 patients (34.48%).

Table 2. Comparison of clinical characteristics between Cirrhotic Patients With and Without Esophageal Varices (n = 29)

Variable	Frequency (%); Mean ± SD;		
	No Varices (n = 10)	**With Varices (n = 19)**	**P-Value**
Age	61.5 ± 14.24	55.5 ± 13.6	0.284
Sex			0.242
Male	4 (40)	12 (63.1)	
Female	6 (60)	6 (31.5)	
Etiology			0.434
HBV	5 (50)	11 (57.8)	
NAFLD	3 (30)	2 (10.5)	
Alcoholic	0	0	
Others	2 (20)	6 (31.5)	
With malignancy	2 (20)	4 (21.0)	0.687
Laboratory findings			
ALT	45.3 ± 32.24	54.63 ± 44.23	0.563
Bilirubin	5.35 ± 2.30	4.9 ± 7.6	0.443
Platelet count	135.2 ± 54.39	138.73 ± 86.5	0.908
INR	1.30 ± 0.40	1.32 ± 0.28	0.865
Creatinine	0.86 ± 0.26	0.91 ± 0.89	0.846
Na	134.5 ± 9.23	137.42 ± 4.41	0.255
Spleen diameter	11.24 ± 3.92	12.95 ± 3.11	0.208
MELD score	15.5 ± 8.30	15.1 ± 7.92	0.901
Spleen Stiffness	5.24 ± 1.02	15.2 ± 9.4	**0.003**

Table 2 provides a summary comparison of clinical characteristics between cirrhotic patients with varices and those without varices. No significant difference was observed in laboratory findings, Spleen Diameter and MELD scores between patients with and without esophageal varices. Spleen Stiffness

was significantly higher in patients with esophageal varices compared to those without varices (p = 0.003).

Table 3. Comparison of clinical characteristics between Cirrhotic patients

	No Varies (n=10)	Grade 1 (n=5)	Grade 2 (n=7)	Grade 3 (n=7)	P-value
	Frequency (%); Mean ± SD; Median (IQR)				
Age	61.5 ± 14.24	55.4 ± 7.92	61.29 ± 13.70	50 ± 16.05	0.335
Sex					0.425
Male	4 (40)	4 (80)	5 (71.43)	3 (42.86)	
Female	6 (60)	1 (20)	2 (28.57)	4 (57.14)	
Etiology					
HBV	5 (50)	4 (80)	5 (71.43)	2 (33.33)	0.328
NAFLD	3 (30)	0	1 (14.28)	1 (14.28)	0.672
Alcoholic	0	0	0	0	-
Others	2 (20)	1 (20)	1 (14.28)	4 (57.14)	0.347
With malignancy	2 (20)	2 (40)	2 (28.57)	0	0.410
Laboratory findings	45.3 ± 32.24	84.8 ± 67.85	45.86 ± 34.64	41.33 ± 27.07	0.267
ALT	5.35 ± 2.30	8.72 ± 5.10	2.81 ± 1.07	4.65 ± 2.92	0.634
Bilirubin	135.2 ± 54.39	170.6 ± 78.06	142.71 ± 107.28	112 ± 71.61	0.642
Platelet count	1.30 ± 0.40	1.45 ± 0.30	1.30 ± 0.37	1.23 ± 0.19	0.748
INR	0.86 ± 0.26	1.34 ± 0.77	0.74 ± 0.26	0.79 ± 0.25	0.536
Creatinine	134.5 ± 9.23	136.6 ± 2.07	137 ± 4.04	139.67 ± 5.64	0.516
Na					
Spleen diameter	11.24 ± 3.92	11.58 ± 2.53	11.44 ± 1.97	15.46 ± 3.08	**0.048**
MELD score	15.5 ± 8.30	20.2 ± 10.76	13 ± 5.72	13 ± 8	0.447
Spleen elastography	5.24 ± 1.02	7.04 ± 3.66	12.21 ± 5.03	24.04 ± 8.87	**<0.001**

Table 3. shows that there a significant difference among four grades of esophageal varices in terms of Spleen diameter (p=0.048) and Spleen elastography (p=<0.001).

Table 3 Summarized the clinical characteristics between cirrhotic patients according to degree of esophageal varices. All groups are comparable in demographics and clinical profile. There was noted significant difference among four groups in terms of spleen diameter (p = 0.048) and Spleen elastography (p= <0.001). Post hoc Tukey HSD done shows significant difference between Spleen Stiffness of patients with no varices and Grade 3 varices (P = <0.01) but no statistical significance between Patients with no varices compared to patients with Grade 1 and Grade 2 varices (p= 0.89 and

p= 0.055 respectively). There were significant differences in patients with Grade 3 varices when compared individually to those patients with grade 2 (p= <0.01) and grade 1 (p = <0.01). However, no significant difference was observed between patients with grade 1 and grade 2 varices (p= 0.353).

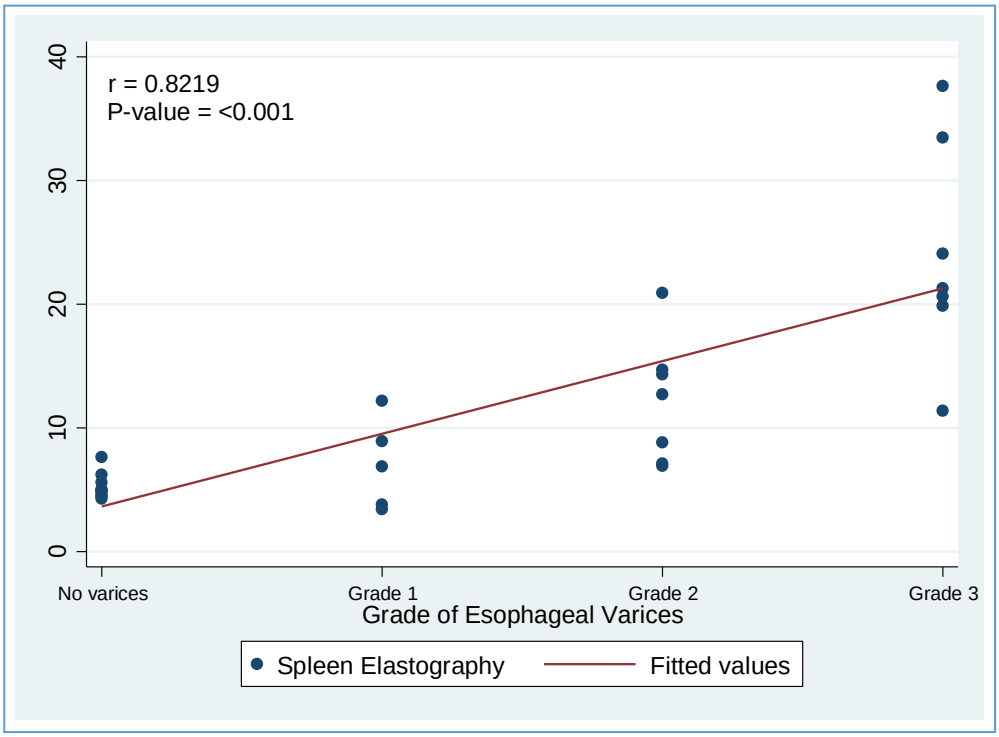

Figure 1. Scatter plot of Spleen elastography and Grade of esophageal varices

There was a very strong direct correlation (Fig. 1) of Spleen elastography and presence and severity of esophageal varices (r = 0.821, p= 0.001). Likewise, Spleen diameter and severity of esophageal varices were directly correlated but to a lesser degree (r= 0.446, p= 0.01).

DISCUSSION

The outcomes of this study showed that patients with esophageal varices had a higher value of Spleen stiffness compared to those patients without varices. Spleen stiffness was likewise increased in patients with endoscopically larger varices. These findings were consistent with the results of Kim et. Al (2015) which showed that spleen stiffness measured by ARFI elastography was effective in detecting varices and in predicting the presence of high risk varices. The strong direct correlation of spleen stiffness and variceal size underscore the possibility of its' use as a safe, affordable and easily accessible noninvasive tool in the diagnosis of Esophageal varices in patients with cirrhosis.

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[2]. These changes may be better observed through elastography and may be better reflective of complex hemodynamic changes observed in portal hypertension, as already reported by other investigators.[3,5]

Although splenomegaly is a relatively common finding in patients with cirrhosis and portal hypertension, the relationship between spleen size and esophageal varices is conflicting. A recent meta-analysis done by Dujunco et. al (2017) concluded that Liver stiffness, Spleen diameter and Platelet count ratio score cannot replace gastroscopy in determining the presence of Esophageal varices with a pooled sensitivity of 69%. Similarly, our findings suggest a direct relationship between spleen diameter and esophageal variceal

size, but correlation remains weak. Spleen size also did not produce a significant difference in between groups of variceal size. This would preclude its use in predicting and monitoring esophageal varix progression.

The main limitations of the current study include the small sample size with a mostly homogenous etiologic cause of liver cirrhosis. A Larger sample size and varied etiologic causes of cirrhosis may produce a different result as Spleen Stiffness values may be different for esophageal varices prediction with different causes of portal hypertension[8]. Determination of diagnostic accuracy was also not done due to the small sample size.

CONCLUSION

In conclusion, the results of this study provide insight to the diagnostic potential of Splenic Stiffness in the screening of esophageal varices in patients with liver cirrhosis. Spleen Stiffness may prove to be a reliable, non-invasive and cost-effective method of variceal screening; especially in the Philippine setting where endoscopy units are scarce and health-care costs are high. The use of spleen elastography should be considered in patients with cirrhosis as it may help identify patients at risk for having Esophageal varices, particularly large varices, and may aid in the more judicious use of upper GI endoscopy as well as alleviate healthcare costs.

RECOMMENDATIONS

To validate the results of the current study, a large scale prospective study is warranted. A larger population size would also allow for determination of diagnostic accuracy of splenic elastography and determination of cut-off values of spleen stiffness in grading esophageal varix severity.

Ethical Considerations

1. Informed Consent, Confidentiality and Security of Information

    Permission and approval from the Institutional Ethics and Review Board (IERB) was obtained prior to the start of the study. Before the commencement of data collection, all participants were fully informed of the purpose and methods of the study and all participants were asked their willingness to participate in the study. Participants were asked to sign an informed consent form.

    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 investigators. The code assigned to each patient was used to track the date and keep the patient anonymous. All personal data will be kept in a secure location under lock and key. Confidential information will not be shared during the publication of the research.

2. Non-maleficence

    Non-maleficence was practiced throughout conduct of the study. All participants were equally informed of the study design and given the choice to not participate should they deem any activity or question to be offensive. Patients that did not participate in the study were provided with the established standard treatment available at the Department of Medicine.

    There were no observed adverse effects to both ultrasound and upper GI endoscopy during the duration of the study period.

3. Beneficence

    Once procedures were completed, appropriate treatment was given depending on the findings of the EGD and Spleen Elastography. The data

and results of this study may produce a safe, effective and affordable alternative screening test to diagnose esophageal varices that may be readily available to the local communities.

4. Plagiarism

   All source materials were properly cited in the Vancouver Citation style.

5. Disclosures: None

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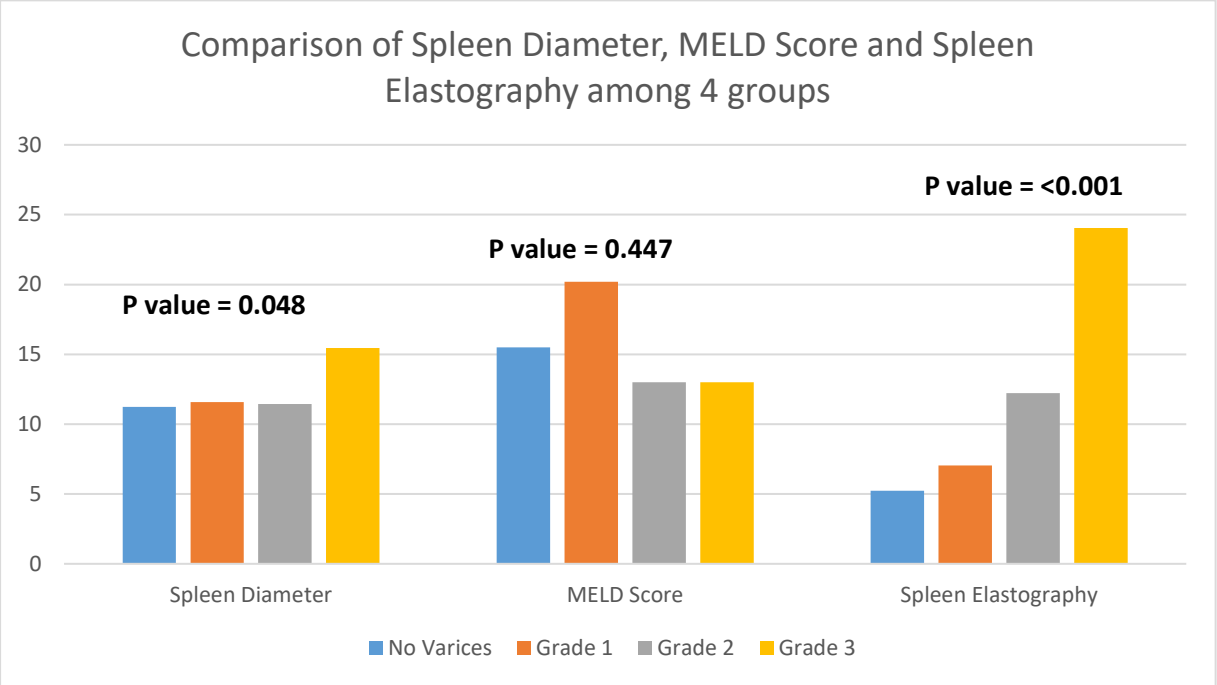
APPENDIX


Comparison of Spleen Diameter, MELD Score and Spleen Elastography among 4 groups
30
25
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P value = 0.048
P value = 0.447
P value = <0.001
Spleen Diameter
MELD Score
Spleen Elastography
No Varices
Grade 1
Grade 2
Grade 3