Liver and Spleen Stiffness by Shear Wave Elastography For A Noninvasive Evaluation of Esophageal Varices in Chronic Liver Disease Patients

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Abstract: Background: Esophagogastroduodenoscopy (EGD) is the gold standard for detecting esophageal varices (EV) in patients with chronic liver disease (CLD). However, due to the possible limitations of EGD, there has been much interest in the use of noninvasive techniques for this purpose. The aim of this study was to evaluate the use of liver and spleen stiffness measured by ultrasound shear wave elastography (LS-SWE, SS-SWE) in prediction of presence and grading of EV in CLD. **Methods:** One hundred-twenty CLD patients were included in this cross-sectional study and subjected to EGD and LS-SWE and SS-SWE after informed consent. Either absence or the grade of EV if present was correlated with values of LS-SWE and SS-SWE. Univariate and multivariate analysis of data and areas under the receiver operating characteristic curve (AUC) were used. **Results:** LS-SWE was better than SS-SWE in detection of EV (AUC of 0.755 vs 0.621) with cutoff values of 10.3 and 18.25 kPa respectively. On the other hand, SS-SWE was better than LS-SWE in discrimination of the EV grade (AUC of 0.865 vs 0.724 for F2 EV, and 0.864 vs 0.713 for F3 EV) with cutoff values of 19.62 and 14.21 kPa respectively for F2 EV and 28.75 and 15.6 kPa respectively for F3 EV. **Conclusion:** LS-SWE and SS-SWE could be considered as a choice noninvasive method for screening EV by sparing EGD for patients in need for intervention.
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1. Introduction

Gastroesophagealvarices (GEVs) are considered the most common cause of upper gastrointestinal bleeding (UGIB) in Egypt. It accounts for about 55% of all causes regardless of the original disease, and 75.5% in chronic liver disease (CLD) patients with portal hypertension with a mortality rate of 8.74 - 19.87%.[1- 4] Esophageal varices (EV) constitute about 72% of variceal cases,[3] and so screening for varices in those patients is highly recommended. Although esophagogastroduodenoscopy (EGD) is the gold standard for EV screening, a lot of patients are afraid from undergoing this procedure due to its invasiveness, possible transmission of infections, complications of sedation and its cost.[5] Several non-invasive laboratories and radiological tools are tried to predict the presence of EV in order to diminish the need for unnecessary EGD.[6]

Shear wave elastography (SWE) is one of the most advanced elastography techniques begin to be used after transient elastography (TE) or acoustic radiation force impulse (ARFI). All of them rely on measuring shear waves propagation and allow assessing tissue stiffness in a quantitative way.[7]Some studies were concerned about getting a relation between liver and spleen stiffness with the EV as with progression of the disease, EV begins to develop secondary to portal hypertension and organs become stiffer. Most of them assessing TE[8] and ARFI[9], but a small number of studies investigated SWE which is the motive for this study.

2. Patients and Methods:

This cross-sectional study was conducted at Gastroenterology and Hepatology unit (TGHU), Internal Medicine Department, Tanta University Hospitals and National Liver Institute (NLI), Menoufia University from June 2017 to September 2018, included 122 patients with liver cirrhosis diagnosed according to National Institute for Health and Care Excellence (NICE) guidelines for cirrhosis in over 16s (2016)[10]were recruited from both institutions.

Patients with any of the following criteria were excluded from the study

1) Past history of endoscopic treatment for GEVs, including endoscopic injection and/or ligation that might affect the hemodynamics of the portal circulation, 2) Transjugular intrahepatic portosystemic shunt (TIPS), 3) Presence of a portal vein (PV) thrombus confirmed by ultrasound and color doppler study, 4) Past history of partial splenic embolization or splenectomy, 5) Past history of any liver surgery, 6)

Patients with hepatocellular carcinoma (HCC). Two patients were excluded from this study as they had pleural effusion and cannot hold their breathing sufficiently for liver and spleen stiffness assessment.

All patients were subjected to the following

Thorough history taking, full clinical examination, laboratory investigations including complete blood count, serum bilirubin, serum albumin, liver enzymes (ALT and AST), prothrombin time and activity, blood urea and serum creatinine, pelvi-abdominal ultrasonography were used for assessment of liver texture and size, PV diameter, splenic longitudinal diameter and presence of ascites. Patients were subjected finally to EGD and Ultrasound SWE of liver and spleen. Patients were classified according to Child-Turcotte-Pugh score.[11]

Research ethics committee, faculty of medicine in Tanta University approved this study with approval code 31526/05/17, all patients were aware of its steps, and goal and they were included after obtaining a written informed consent from them.

EGD:

All patients were subjected to EGD for screening for varices either at TGHU or NLI to detect presence or absence of GEVs and determine its degree if present. They classified into four groups as follow, control group (CG) (n= 30) were chronic liver disease (CLD) patients with no varices (F0), group 1 (G1) (n= 30) were CLD patients with F1 varices, group 2 (G2) (n= 30) were CLD patients with F2 varices and group 3 (G3) (n= 30) were CLD patients with F3 varices. According to general rules for recording endoscopic findings of GEVs,[12] EV were categorized as straight and small (F1), moderately enlarged and beady (F2), or markedly enlarged with a nodular or tumor-like shape (F3). Liver and spleen SWE that was done 3-5 days after EGD.

Liver and spleen SWE:

Liver and spleen stiffness assessment were performed at NLI using iU22 ultrasound system (iU22, Philips Medical systems, Bothell, WA, USA), which can assess stiffness by shear wave with elastography point quantification (ElastPQ) feature. SWE examination was done with a convex transducer C5-1 (1-5 MHz; C5-1, Philips Healthcare) through intercostal route in a supine position with the corresponding arm maximally abducted to widen intercostal space for better examination. Some patients underwent SWE in left or right lateral position for better access to liver or spleen respectively with holding their breath during time of examination for about 5 seconds. The maximum penetration depth of ElastPQ was 8 cm and the region of interest (ROI) was presented as a rectangular area measured 5 x 15 mm. It was placed at about 1.5 - 3 cm from the capsule of liver or spleen over an area of the parenchyma devoid of large blood vessel or biliary ducts and away from the heart or other organs like the kidney. We considered the mean value of 10 valid successful measurements (out of about 20 – 25 attempts) expressed in kilopascals (kPa) for each organ which is automatically reported and calculated as sample report documenting 10 measurements and their average (mean), standard deviation and median values. In the liver they were taken at different areas at right lobe and in the spleen, they were taken from upper and lower poles and from the mid part.

Statistical analysis:

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0**.** **(**Armonk, NY: IBM Corp**)** Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using mean and standard deviation. The following tests were used:

1 - Chi-square test for categorical variables, to compare between different groups.

2 - Monte Carlo correction for chi-square when more than 20% of the cells have expected count less than 5.

3 - F-test (ANOVA) for normally distributed quantitative variables, to compare between more than two groups, and Post Hoc test (Tukey) for pair wise comparisons.

4 – Kruskal Wallis test for abnormally distributed quantitative variables, to compare between more than two studied groups, and Post Hoc (Dunn's multiple comparisons test) for pair wise comparisons.

Significance of the obtained results was judged at the 5% level.

3. Results:

A total of 120 patients were included in this study, epidemiological, clinical, laboratory and radiological data are summarized in tables 1 and 2, and showed statistically significant difference between groups in age, serum bilirubin, serum albumin, AST, INR, platelet count, Child Pugh score, spleen diameter and ascites.

Liver stiffness and its correlation with EV, liver size, portal and splenic vein diameter:

We considered the mean value of liver stiffness using SWE (LS-SWE) measurements in all patients and we found that there was a concomitant increase in LS-SWE with higher EV grade, with statistically significant difference among the four groups (P <0.001) as shown in table 3.

Table (1): Patients' characteristics

Parameter	CG *(n=30)*	G 1*(n=30)*	G 2*(n=30)*	G 3*(n=30)*	P- value
M:F ratio	19:11	20:10	19:11	23:7	0.652
Age	51.13 ± 9.11	58.20 ± 10.02	54.87 ± 8.90	58.37 ± 8.65	0.008*
Etiology of CLD					
HCV	25	27	25	26	0.775
HBV	5	-	-	-	0.020*
Mixed HCV and HBV	-	-	3	-	0.045*
Bilhariziasis	-	-	2	1	0.618
NAFLD	-	1	-	1	0.840
AIH	-	1	-	-	1.000
Undetermined	-	1	-	2	0.620

Table (2): Laboratory, radiological findings and Child Pugh score of the studied patients

Parameter	CG *(n=30)*	G 1*(n=30)*	G 2*(n=30)*	G 3*(n=30)*	P-value
Bilirubin (mg/dl)	1.18 ± 0.47	1.49 ± 0.70	1.53 ± 0.79	1.99 ± 0.88	<0.001*
Albumin (g/dl)	4.08 ± 0.42	3.45 ± 0.51	3.44 ± 0.54	3.15 ± 0.43	<0.001*
AST (IU/L)	29.10 ± 11.37	43.49 ± 31.51	42.37 ± 35.24	35.59 ± 14.47	0.002*
ALT (IU/L)	23.17 ± 11.50	33.54 ± 40.62	36.83 ± 33.34	26.06 ± 10.41	0.076
INR	1.09 ± 0.12	1.29 ± 0.19	1.31 ± 0.22	1.45 ± 0.23	<0.001*
Platelet count (/cmm) ($\times 10^3$)	117.5 ± 29.55	104.4 ± 45.51	99.07 ± 43.28	98.87 ± 41.48	0.006*
Child Pugh score (A /B /C)	28/2/0	20/10/0	21/6/3	14/10/6	0.001*
Ultrasound findings					
Liver size (cm)	14.43 ± 0.90	14.07 ± 1.41	14.07 ± 0.91	13.86 ± 1.33	0.298
Portal vein diameter (mm)	13.54 ± 1.60	13.89 ± 2.22	14.18 ± 2.24	14.29 ± 3.30	0.636
Spleen diameter (cm)	16.31 ± 2.34	17.17 ± 2.52	18.42 ± 2.51	17.97 ± 1.98	0.004*
Splenic vein diameter (mm)	10.85 ± 1.38	10.94 ± 2.47	10.61 ± 1.88	11.50 ± 2.09	0.162
Ascites	1	4	4	11	0.001*

Table (3): Comparison between the different studied groups according to LS-SWE

LS-SWE (kPa)	CG *(n=30)*	G 1 *(n=30)*	G 2 *(n=30)*	G 3 *(n=30)*	P
Mean ± SD.	9.40 ± 3.38	12.02 ± 1.34	14.73 ± 4.55	18.07 ± 4.21	<0.001*
p_1		0.028*	<0.0001*	<0.0001*	
Sig bet. Groups		p_2=0.022*, p_3<0.001*, p_4=0.003*			

Pairwise comparison bet. each 2 groups was done using **Post Hoc Test (Tukey)**

p: p value for comparing between the different groupsp_1: p value for comparing between the group 0 and each other group

p_2: p value for comparing between groups 1 and group 2p_3: p value for comparing between groups 1 and group 3

p_4: p value for comparing between groups 2 and group 3*: Statistically significant at $p \leq 0.05$

There was no significant correlation between LS-SWE and liver size, PV or splenic vein diameter in all patients' groups except in F2 EV group there was a significant negative correlation between LS-SWE and liver size as shown in table 4.

Table (4): Correlation between LS-SWE mean with liver size and PV in each group

Parameter	CG *(n=30)*		G 1*(n=30)*		G 2*(n=30)*		G 3*(n=30)*	
	R	p	r	p	r	p	r	p
Liver size	-0.142	0.454	0.172	0.362	-0.410	0.024*	-0.086	0.652
PV	-0.013	0.948	-0.218	0.248	0.170	0.368	0.087	0.649
Spleen vein	0.064	0.736	-0.036	0.849	-0.033	0.862	-0.200	0.290

r: Pearson coefficient *: Statistically significant at $p \leq 0.05$

Spleen stiffness and its correlation with varices grade, splenic longitudinal diameter and splenic vein diameter:

As in LS-SWE, we considered the mean value for spleen stiffness using SWE (SS-SWE) and it showed a concomitant increase with higher grades of EV. There was a statistically significant difference in between four groups (P <0.001) as shown in table 5.

Table (5): Comparison between the different studied groups according to SS-SWE

SS-SWE	CG *(n=30)*	G 1 *(n=30)*	G 2 *(n=30)*	G 3 *(n=30)*	P
Mean ± SD.	15.87 ± 1.95	17.91 ± 5.50	23.79 ± 3.34	32.41 ± 7.25	<0.001*
p_1		0.386	<0.001*	<0.001*	
Sig bet. groups		p_2<0.001*, p_3<0.001*, p_4<0.001*			

Pairwise comparison bet. both 2 groups were done using **Post Hoc Test (Tukey)**

p: p value for comparing between the different groups p_1: p value for comparing between the group 0 and each other group

p_2: p value for comparing between groups 1 and group 2p_3: p value for comparing between groups 1 and group 3

p_4: p value for comparing between groups 2 and group 3*: Statistically significant at p ≤ 0.05

As regards the correlation between SS-SWE and splenic longitudinal diameter splenic vein and PV diameter, there were statistically significant positive correlations between SS-SWE and splenic longitudinal diameter in G 2 (p 0.018) and between SS-SWE and PV diameter in G1 and G2 (p 0.016 and 0.001) as demonstrated in table 6.

Table (6): Correlation between SS-SWE mean with splenic longitudinal diameter, splenic vein diameter and PV

Parameter	CG *(n=30)*		G 1 *(n=30)*		G 2 *(n=30)*		G 3 *(n=30)*	
	r	p	r	p	r	P	r	p
Spleen size	0.091	0.632	0.088	0.643	0.428	0.018*	0.022	0.909
Spleen vein	0.286	0.125	-0.101	0.595	0.285	0.127	0.225	0.231
PV	0.177	0.349	0.437	0.016*	0.563	0.001*	0.030	0.877

r: Pearson coefficient *: Statistically significant at p ≤ 0.05

Prediction of presence of EV:

The detection of EV was univariately correlated to age, etiology of HBV, splenic size, total serum bilirubin, serum albumin, AST, INR, Child Pugh class B and C, all with p value less than 0.05 and also correlated to both LS-SWE (p <0.001) and SS-SWE (p <0.001). In multivariate analysis for detection of any EV, it was independently correlated with LS-SWE (p 0.004), SS-SWE (p 0.011) and total serum bilirubin (p 0.017) but not with spleen size (p 0.711) or Child Pugh class b or C (p 0.200) as shown in table 7.

Table (7): Multivariate analysis for discrimination of any EV from no EV cases

	Multivariate	
	P	OR (95%C.I)
Age (years)	**0.119**	1.138(0.967 – 1.338)
HBV	**0.021***	0.0(0.0 – 0.287)
Spleen size (cm)	**0.711**	0.847(0.352 – 2.039)
Total Bilirubin (mg/dl)	**0.017***	0.001(0.0 - 0.305)
Albumin (g/dL)	**0.232**	0.141(0.006 – 3.507)
AST (IU/L)	**0.226**	1.086(0.950 – 1.241)
INR	**0.783**	6.831(0.0 - 5821879.57)
Child classification (B+C)	**0.200**	230.259(0.056 - 940766.7)
LS-SWE mean	**0.004***	2.963(1.405 – 6.247)
SS-SWE mean	**0.011***	1.860(1.153 – 3.001)

OR: Odd`s ratio. C.I: Confidence interval,**: Statistically significant at p ≤ 0.05**

N.B: All variables with p <0.05 was included in the multivariate

Receiver operating characteristics analysis (ROC) for prediction of any EV presence in CLD patients confirms superiority of LS-SWE to SS-SWE with an area under the curve (AUC) of 0.755 and 0.621 respectively. The optimal cutoff value for LS-SWE is 10.3 kPa (sensitivity, 93.33%; specificity, 63.33%) and 18.25 kPa for SS-SWE (sensitivity, 36.67%; specificity, 93.33%) (Table 8 and fig 1).

Diagnostic accuracy of LS-SWE and SS-SWE in grading of EV:

Receiver operating characteristics analysis (ROC) for prediction of EV degree in CLD patients confirms superiority of SS-SWE to LS-SWE for both F2 and F3 with an area under the curve (AUC) of 0.865 and 0.724 respectively for F2 and 0.864 and 0.713 respectively for F3. The optimal cutoff value for

SS-SWE is 19.62 kPa for F2 (sensitivity, 90%; specificity, 80%) and 28.75 kPa for F3 (sensitivity, 73.33%; specificity, 93.33%). LS-SWE cutoff values were 14.21 kPa for F2 (sensitivity, 46.67%; specificity, 96.67%) and 15.6 kPa for F3 (sensitivity, 80%; specificity, 66.7%) (Table 8 and fig 2,3).

Table (8): Agreement (sensitivity, specificity) for LS-SWE and SS-SWE mean to diagnose esophageal varices degree.

	AUC	P	95% C.I		Cut off	Sensitivity	Specificity	PPV	NPV
			LL	UL					
Diagnosis of F1 EV									
LS-SWE mean	0.755	0.001*	0.625	0.885	>10.3	93.33%	63.33%	71.8%	90.5%
SS-SWE mean	0.621	0.109	0.476	0.765	>18.25	36.67%	93.33%	84.6%	59.6%
Diagnosis of F2 EV									
LS-SWE mean	0.724	0.001*	0.59	0.83	>14.21	46.67%	96.67%	93.3%	64.4%
SS-SWE mean	0.865	<0.001*	0.75	0.94	>19.62	90.0%	80.0%	81.8%	88.9%
Diagnosis of F3 EV									
LS-SWE mean	0.713	0.002*	0.581	0.822	>15.6	80.0%	66.7%	70.6%	76.9%
SS-SWE mean	0.864	<0.001*	0.751	0.939	>28.75	73.33%	93.33%	91.7%	77.8%

AUC: Area Under a Curve, CI: Confidence Intervals, P value: Probability value, PPV: positive predictive value, NPV negative predictive value

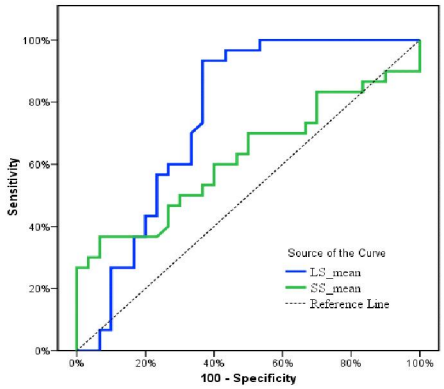

Figure (1): ROC curve for LS-SWE and SS-SWE to diagnose patients with F1 esophageal varices from no esophageal varices

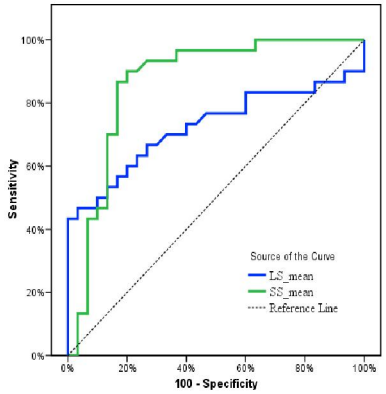

Figure (2): ROC curve for LS-SWE mean and SS-SWE mean to diagnosis patients with F2 from F1 esophageal varices

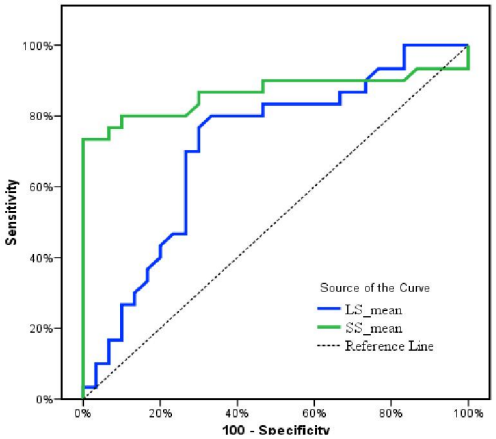

Figure (3): ROC curve for LS-SWE mean and SS-SWE mean to diagnosis patients with F3 from F2 esophageal varices

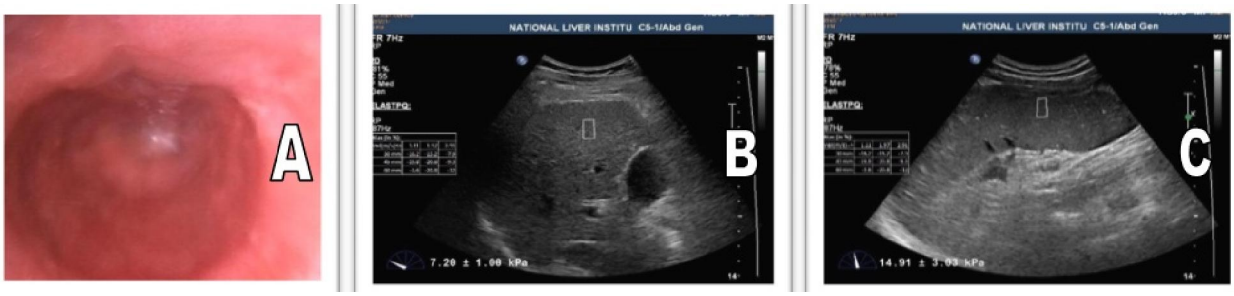

Figure (4): a sample images of grade F0 EV with (A) endoscopic image, (B) liver stiffness value of 7.20±1.00 kPa using Elast PQ SWE, and (C) spleen stiffness value of 14.91±3.03 kPa using Elast PQ SWE.

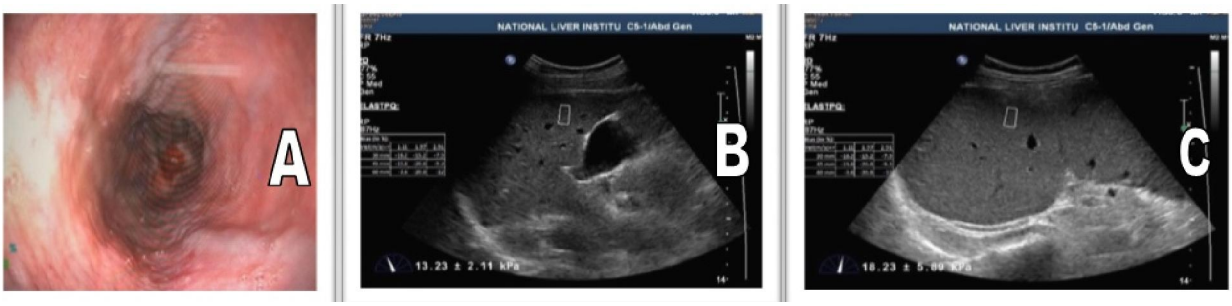

Figure (5): a sample images of grade F1 EV with (a) endoscopic image, (b) liver stiffness value of 13.23±2.11 kPa using Elast PQ SWE, and (c) spleen stiffness value of 18.23±5.89 kPa using Elast PQ SWE.

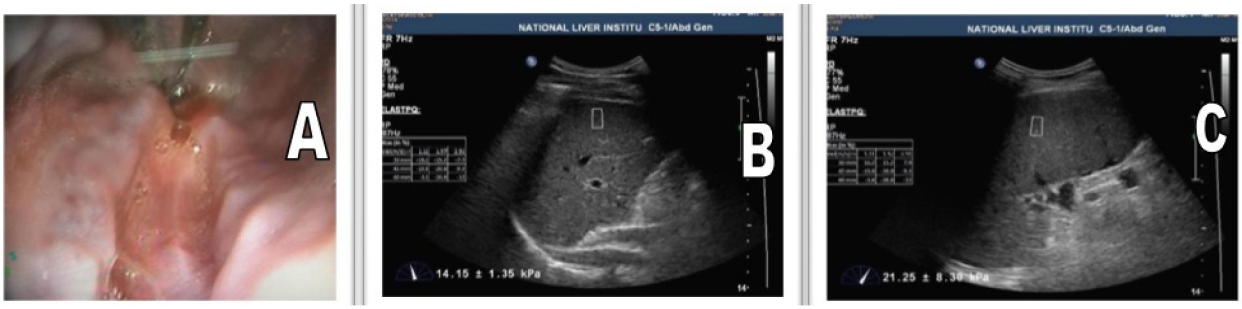

Figure (6): a sample of grade F2 EV with (a) endoscopic image, (b) liver stiffness value of 14.15±1.35 kPa using Elast PQ SWE, and (c) spleen stiffness value of 21.25±8.30 kPa using Elast PQ SWE.

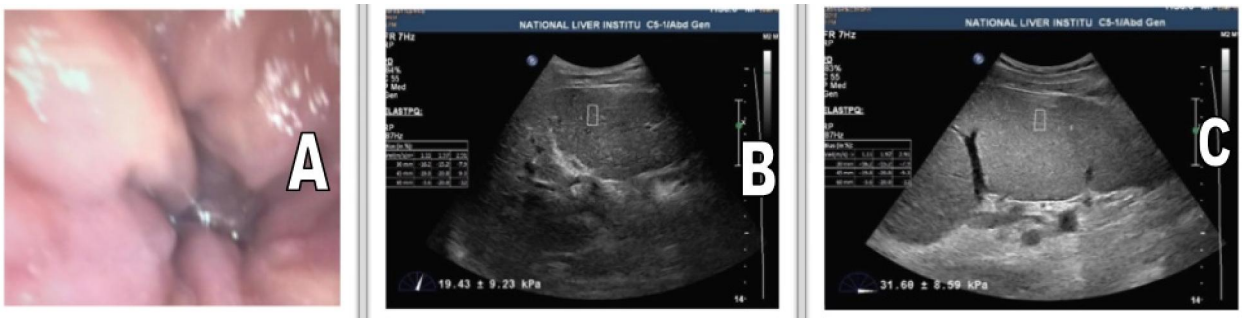

Figure (7): a sample of grade F3 EV with (a) endoscopic image, (b) liver stiffness value of 19.43±9.23 kPa using Elast PQ SWE, and (c) spleen stiffness value of 31.60±8.59kPa using Elast PQ SWE.

4. Discussion:

The aim of this study was to assess LS and SS using ultrasound SWE as non-invasive methods to predict EV presence and its grade if present in CLD patients. We considered SS assessment, as it is a direct predictor of portal hypertension degree because it is simply congested. On the other hand, increased LS owes to increase both intrahepatic resistance and portal venous blood flow.[13] We used ultrasound SWE because it is a recent method for organ stiffness assessment and incorporated in usual ultrasound machines. The second advantage is lacking the drawbacks of transient elastography (TE); although it's wide spread and availability; its use is limited for obese patients and those with ascites, so ascetic patients were included in our study. Another advantage, the region of interest of SWE is smaller than that of TE (0.5 x 1.5 cm. versus 1x 4 cm) and can be moved under sight helping to select parenchymal region devoid of blood vessels.[14]We found that for prediction of EV presence (fig 4,5), LS-SWE is better than SS-SWE (AUC was 0.755 and 0.621 respectively) with a cut off value of 10.3 kPa for LS-SWE (sensitivity, 93.33%; specificity, 63.33%) and 18.25 kPa for SS-SWE (sensitivity, 36.67%; specificity, 93.33%). On the other hand, SS-SWE was better in discriminating the grade of EV than LS-SWE (fig 6,7) with SS-SWE cut off value of 19.62 kPa for F2 EV (sensitivity, 90%; specificity, 80%) and 28.75 kPa for F3 EV (sensitivity, 73.33%; specificity, 93.33%), while LS-SWE cutoff values were 14.21 kPa for F2 EV (sensitivity, 46.67%; specificity, 96.67%) and 15.6 kPa for F3 EV (sensitivity, 80%; specificity, 66.7%). Moreover, along our study, SS-SWE was always higher than LS-SWE for the same patient. This finding is due to that 75% of liver blood supply is derived from portal circulation which is a part of venous system with low pressure but spleen is exclusively supplied by splenic artery with a higher pressure.[15]

Our results are agreed with two studies compared LS and SS by SWE with LS and SS using TE for prediction of clinically significant portal hypertension (CSPH). One of them concluded that LS by SWE is better than the other three stiffness methods (AUC was 0.939 with cut off value 15.4),[16] and the other one showed that LS-SWE cut off value for detection of CSPH is 24.6 kPa with AUC 0.87).[17]Morisaka et al used magnetic resonance elastography (MRE) to assess SS and LS and concluded that both LS and SS were associated with prediction of EV but SS was strong associated with severe EV.[18] Another study indicated that LS is better than SS in prediction of CSPH (AUC were 0.9 versus 0.68) but stiffness was measured in meters/second (m/s) using acoustic radiation force impulse (ARFI).[19] For studies utilizing TE for SS assessment, recent two studies indicated that SS can be used for prediction of large or high risk EV. One of them introduced a novel TE examination for SS to increase the availability of TE systems to detect the high values of SS. Its results (cut off value 50.3 kPa, AUC 0.81).[20] and the other used SS cut off value of 46 kPa in conjunction with Baveno IV criteria (LS by TE < 20 kPa and platelet count < 150,000/cmm in compensated cirrhosis did not indicate endoscopic screening for varices) to either rule in or out high risk EV with (AUC= 0.847 and high sensitivity 97.8%).[21]

On the contrary, some studies conclude superiority of splenic stiffness in prediction of any EV. Ma et al stated superiority of SS over LS in prediction of EV presence in CLD patients with summary receiver operating characteristic (SROC) curve values of 0.88 versus 0.81 for SS and LS respectively.[22]It may be attributed to that comparing results obtained by the different elastography techniques is challenging because terminology, reported parameters, shear wave frequency, and other technical factors are not standardized. [23]

Ye et al concluded high performance of SS measured by ARFI in determination of both presence and grading of EV in patients with chronic hepatitis B which is against our results and it may belong to single etiology of CLD in all studied patients.[24]

Although this study is one of the fewest studies regarding this issue in Egypt, [25] however, there are some limitations in this study. First, it includes CLD patients with heterogeneous etiologies with unequal percentages of patients that may affect the values of liver stiffness as the pathological processes are quite different. In addition to, that some etiologies tend to cause splenomegaly more than other with subsequent splenic stiffness affection. It needs to be a multicenter study to include larger number with nearly equal distribution of etiologies. Second, LS and SS were used in this study to detect EV in relation to its size and did not record other risky signs as cherry red spots over varices.

Lastly, although SS is still limited in its clinical use because of different cut off values, and techniques, we concluded superiority of LS over SS measured by ultrasound SWE in prediction of EV presence, on the other hand, SS is more valuable in grading EV and all of these findings can decrease performing unnecessary EGD and spare it for patients in need for endoscopic interventions.

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Declaration of conflicting interest:

The authors declare that there is no conflict of interest.

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