Kufa Medical Journal | Vol. 20, No. 1, 2024

Original Article | DOI: https://doi.org/10.36330/kmj.v20i1.15362

p-ISSN: 1993-517X

e-ISSN: 2709-4464

Shear-Wave Elastographic Evaluation of Splenic Stiffness in Patients with Chronic Liver Diseases as A Predictor of The Oesophageal Varices Grade

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ABSTRACT

Background: *Chronic Liver disease (CLD) is a global public health problem and one of the leading causes of mortality worldwide with many complications like portal hypertension (PH) and esophageal varices (EV). Researchers have investigated the role of shear-wave elastography (SWE) as a non-invasive method to assess patients with cirrhosis and PH. However, studies evaluating the role of splenic stiffness (SS) have shown variable results.* ***Aim of the study:*** *This study aims to assess the SS in a patient with CLD compared to controlled cases and to evaluate its role in the prediction of EV grade.*

Patients and methods: *The study included 60 participants; 30 patients diagnosed with CLD by the clinical, laboratory, and radiological investigation, who underwent upper gastrointestinal endoscopy; and 30 control health individuals. The mean splenic size, SS, and platelet counts were measured for all participants. Mean SS was compared between two groups, and then its validity in differentiated between low and high-risk groups of EV was assessed.*

Results: *Patients with CLD and controls were significantly different in SS values with cut-off value of 12.49 Kpa. Among CLD patients, the low and high-risk EV subgroups were significant different in SS values with cut-off value of 15.125 KPa. Compared with splenic size and platelet count, SS had the highest accuracy (93.3%) in predicting high-grade EV.*

Conclusions: *Patients with CLD showed higher SS values than control with stepwise increase in SS with increasing grade of EV. SS can accurately predict high-risk groups of EV hence may help decrease patients' burden by avoiding unnecessary endoscopy.*

Keywords: Chronic liver disease, esophageal varices, splenic stiffness, Ultrasound, shear wave Elastography.

Article Information

Received: March 3, 2024; Revised: May14, 2024; Online: June, 2024

INTRUDUCTION

Chronic Liver disease (CLD) is a global public health problem [1] and one of the leading causes of mortality worldwide [2]. In patients with CLD, complications are mainly related to portal hypertension (PHT) and esophageal varices (EV) [3,4]. PHT carries mortality and recurrence rates and evaluation is important for early treatment and improving outcomes [5,6].

Because EV usually don not cause signs and symptoms unless they bleed, patients are advised to undergo esophagogastroduodenoscopy (OGD) upon diagnosis of cirrhosis [7] being the gold-standard

tool for EV detection [8,9]. Liver biopsy is an accurate test for the diagnosis of CLD, but is invasive and generally less reliable in the assessment of complications [10],[11].

Hepatic vein portal gradient (HVPG) is an excellent predictor of clinical decompensation [12], but is an invasive and technically difficult procedure [13]. Therefore, non-invasive methods have been recently developed, but were proved inaccurate for the early prediction of clinical decompensation in cirrhotic patients[14,15]. Two-dimensional shear wave elastography (2D-SWE) has emerged as the most frequently used diagnostic ultrasound tool for hepatic fibrosis quantification by measuring liver stiffness (LS) [16,17] and was found to correlate well with HVPG and can detect clinically significant PHT[18], but the measurements can be compromised by several practical considerations [19] [20].

Splenic elastography has been also used in patients with CLD [21,22,23] and splenic stiffness (SS) values were found to correlate well with the stage of liver fibrosis [24] and PHT [25]. However previous studies have either concluded variable cut-off values of SS or included only patients with certain etiology of CLD and there was no emphasis on the EV grading. Therefore, the current study was conducted to assess the SS values in patient with CLD of different aetiologies and to evaluate the value of SS in the prediction of EV grade.

PATIENTS AND METHODS

This case-control study was conducted on 60 participants (30 CLD patients with PHT and 30 healthy control) at the Radiology department of Al-Sadir Medical City / Annajaf Health Directorate, from February 2022 to February 2023.

The Study Design

It is a case-control study.

Subjects

The following cases were excluded: 1) patients with a history of intervention for PHT (splenic embolization, trans jugular intrahepatic shunt, splenectomy, etc.) or splenic and hepatic surgery; 2) unproved diagnosis of EV because of an unavailable EG report; 3) presence of technical difficulty due to cooperation, inability to hold breath, ongoing gastrointestinal hemorrhage, hemodynamic instability, severe ascites, severely decompensated liver disease, and an unusual small-sized spleen; and 4) patient with splenic SOL or diffuse enlargement due to underlying infectious, hematological or infiltrative disease. The study was approved by the Intuitional Review Committee and informed consents to participate in the study were taken directly from all participants.

Exclusion criteria

Thirty patients, regardless of age and gender, were recruited from the gastrointestinal center in Al-Sader Medical City with a proven diagnosis of CLD and PHT with EV documented and graded by OGD were selected. They were age-and gender matched with 30 healthy individuals, who have no clinical or laboratory evidence of CLD as control. CLD and PHT were diagnosed and documented by the clinical, laboratory and radiological. OGD

was the gold standard for evaluating PHT and EV diagnosis and grading using Baveno classification [26].

Data collection:

The clinical history and data laboratory investigations and OGD reports were obtained from all the patients directly and /or from their records.

Instruments

All ultrasound and SWE examinations were done by a single radiologist, using LOGIC E9 XDClear ultrasound system (GE Healthcare, 2019, USA) and C1-6 convex probe. All participants were examined after fasting for at least 4 hours. SWE measurements were performed in the supine position, during normal breathing. A rectangular box was placed in the splenic parenchyma, so it did not contain vessels. The SS was calculated by placing a region of interest (ROI) measuring 1.5 × 0.5 cm drawn in the largest possible diameter into the rectangular box (Figure 1). ROI box was placed 1.0 cm below the capsule of the spleen and then adjusted to be in a region free of the blood vessels and rib shadowing. Then the stiffness value was obtained in kilopascals (KPa) and the measurement was validated using Grgurevic method [27]. Three to six valid measurements were taken from the upper, mid, and lower portions of the spleen, and their average was accepted as the mean SS value.

STATISTICAL ANALYSIS

Statistical analysis was carried out using SPSS (version 27). Student t-test was used to compare means between the two groups while ANOVA test was used to compare means among three groups or more. Pearson Chi-Square test was used to find the association between categorical variables. A p-value of ≤ 0.05 was considered significant.

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RESULTS

A total number of 60 participants (30 patients and 30 control) were included and showed no statistically significant difference regarding mean age and gender distribution (table 1).The mean splenic size was (16.17 ± 1.80) cm, the mean SS was (26.84 ± 14.49) KPa and the mean platelet count was (194.77 ± 137.83) (cell x10^3/microliter) as shown in table 2. The mean differences of splenic size, SS, and platelet count were not statistically significant different according to etiology of liver disease Table 4. There was a stepwise increase in SS values and a relative decrease of mean platelet count with an higher grades of EV, with statistically significant difference while no statistically significant difference between mean splenic size and grade of EV was found (table 5). The ROC curve for SS in predicting differentiate cases of liver diseases revealed optimal cut-off value was ≥ 12.49 KPa with overall accuracy of 85.0% (figure 2, A).

For practical purposes and clinical implication, we considered grade I varices as a low-risk group while grad II and III are a high-risk group as these groups have different treatment strategies directed by gastroenterology specialists. The optimal SS cut-off value to predict high-risk groups of EV was ≥ 15.125 KPa , with highest level accuracy in predicting high-risk EV compared to that of platelet count and splenic size as shown in figure 2 (B, C and D) and table 6.

Table 1: shows the association between gender and study group (N=60).

Study variable	Study group		P-value
	Patients	Control group	
Gender			
Male	17 (56.7)	17 (56.7)	1.000
Female	13 (43.3)	13 (43.3)	
Total	30 (100.0)	30 (100.0)	
Age (Mean ± SD years)	51.83 ± 14.97	51.10 ± 17.17	0.861

Table 2. Splenic size, splenic stiffness and platelet count of patients with liver diseases. (N=30)

Study parameters	(Mean ± SD)	Range
Splenic size (cm)	(16.17 ± 1.80)	(13.0-21.0)
Splenic stiffness KPa	(26.84 ± 14.49)	(9.82-55.98)
Platelet count (cell x10^3/microliter)	(194.77 ± 137.83)	(56.0-686.0)

Table 3: Mean splenic size and splenic stiffness values of the study groups

Study variable	Study group	Mean ± SD	P-value
Splenic size (cm)	Patients	16.17 ± 1.80	**<0.001***
	Control group	11.17 ± 1.37	
Splenic stiffness (KPa)	Patients	26.84 ± 14.49	**<0.001***
	Control group	9.33 ± 3.52	

Table 4: The mean differences of study variables according to the type of liver disease (N=30).

Study variables	Type of liver disease	N	Mean ± SD	P-value
Splenic size (cm)	Alcoholic liver disease	9	15.56 ± 1.74	0.316
	Chronic HCV	7	15.86 ± 1.86	
	Cryptogenic CLD	5	17.80 ± 2.17	

	NASH	5	15.80 ± 1.64	
	Primary biliary cirrhosis	2	17.00 ± 0.00	
	Wilson disease	2	16.00 ± 0.00	
Splenic stiffness (KPa)	Alcoholic liver disease	9	27.09 ± 15.05	0.954
	Chronic HCV	7	25.87± 14.43	
	Cryptogenic CLD	5	28.24 ± 19.52	
	NASH	5	25.87 ± 15.45	
	Primary biliary cirrhosis	2	35.05 ± 16.30	
	Wilson disease	2	19.76 ± 5.32	
Splenic stiffness (m/s)	Alcoholic liver disease	9	2.90 ± 0.83	0.961
	Chronic HCV	7	2.81 ± 0.86	
	Cryptogenic CLD	5	2.92 ± 1.05	
	NASH	5	2.83 ± 0.90	
	Primary biliary cirrhosis	2	3.37 ± 0.81	
	Wilson disease	2	2.56 ± 0.35	
Platelet count (cell x 10^3/microliter)	Alcoholic liver disease	9	219.67 ± 108.84	0.888
	Chronic HCV	7	191.29 ± 123.29	
	Cryptogenic CLD	5	220.80 ± 263.40	
	NASH	5	194.00 ± 104.22	
	Primary biliary cirrhosis	2	107.50 ± 41.71	
	Wilson disease	2	119.00 ± 80.61	

Table 5: The mean differences of study variables according to grades of esophageal varices (N=30).

Study variables	Grades of esophageal varices	Number	Mean ± SD	P-value
Splenic size (cm)	Grade I	10	16.70 ± 2.11	0.304
	Grade II	8	15.38 ± 1.77	
	Grade III	12	16.25 ± 1.48	
Splenic stiffness (KPa)	Grade I	10	12.63 ± 1.87	**<0.001**
	Grade II	8	25.94± 9.29	
	Grade III	12	39.27 ± 11.97	
	Grade II	8	2.90 ± 0.55	

	Grade III	12	3.57 ± 0.60	
Platelet count (Cell x10^3/microliter)	Grade I	10	318.30 ± 171.78	**0.001**
	Grade II	8	153.25 ± 47.25	
	Grade III	12	119.50 ± 56.70	

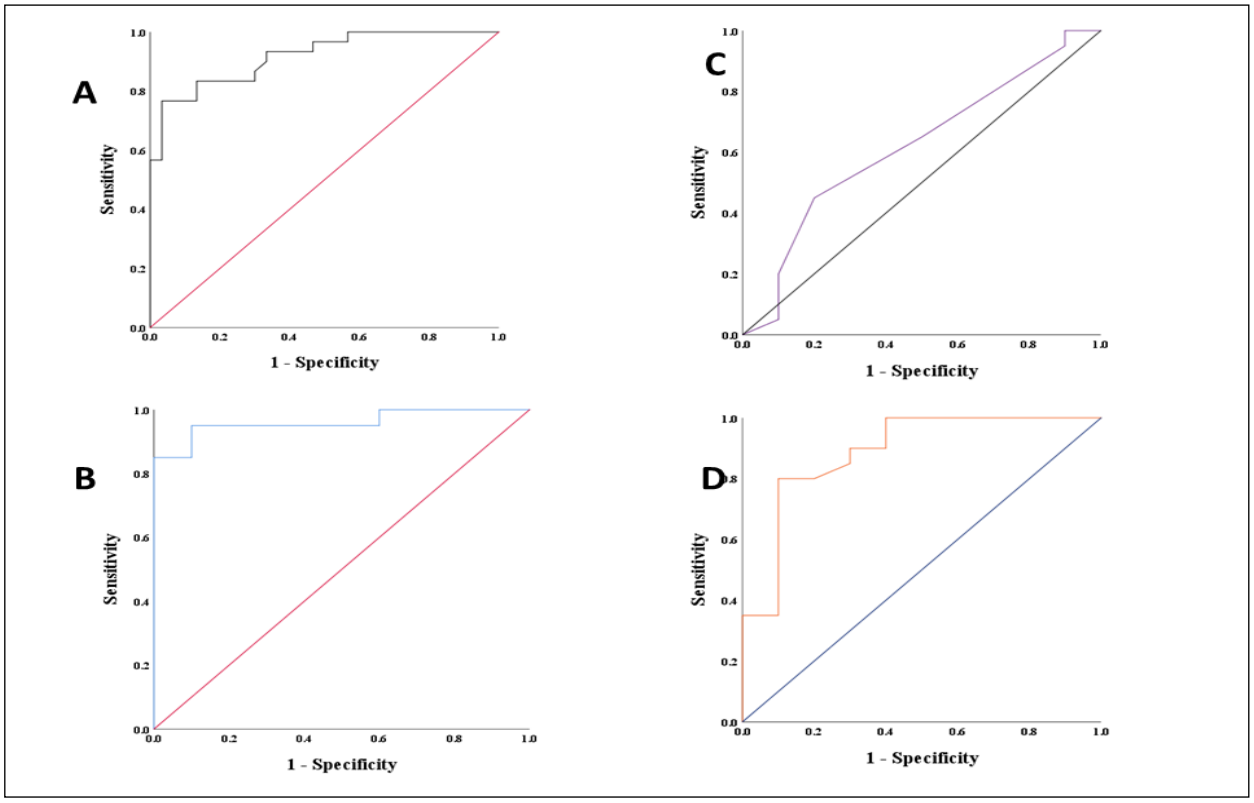

Figure 2: ROC curve of splenic stiffness in predicting liver disease (A). ROC curves of splenic stiffness (B), splenic size (C) and Platelet count to predict high-risk groups of oesophageal varices.

Table 6: The sensitivity, specificity, PPV, NPV, and overall accuracy of study variables to predict high-risk groups of oesophageal varices.

Study variable	Cut-off point	Sensitivity	Specificity	PPV*	NPV**	Overall accuracy
Splenic size (cm)	≤ 16.50	65.0%	50.0%	72.2%	41.7%	60.0%
Splenic stiffness (KPa)	≥ 15.125	95.0%	90.0%	95.0%	90.0%	93.3%
Platelet count (cell x 10^3/microliter)	≤ 173.50	80.0%	90.0%	94.1%	69.2%	83.3%

**PPV= Positive predictive value; **NPV= negative predictive value.*

DISCUSSION

The prediction of the risk of EV can be done using simple parameters like splenic size and platelet counts or more invasively by OGD and HVPG. With the feasibility and recent advances in elastography, researchers have investigated the role of the LS and SS in assessing cirrhosis and PHT because anatomically, the portal vein arises by the confluence of the superior mesenteric and splenic veins; therefore, disorders in portal blood flow may lead to spleen congestion, increasing its stiffness [28] . However, these studies have shown variable results[29]. In this study, the mean elasticity values for the spleen did not exhibit a significant gender or age difference which was in agreement with [30,31] .

The mean SS cut-off value that discriminated between healthy and CLD patients in the current study was 12.49 Kpa while 15.125 Kpa was as a cut-off value that predicted high-risk groups of EV, both values were slightly lower than [32] who found mean SS of 15 KPa in normal subjects and 20.2KPa in patients with CLD complicated by EV.

Considering validity in predicting the presence of EV in patients with CLD, the current study revealed that SS was more accurate in than splenic size and platelet count, a finding that was consistent with [33] with higher overall accuracy in our study. According to findings of current study, we belief that SS can serve as a surrogate for the dynamic component of PHT, with resultant improved discrimination between clinically significant PHT and subsequent EV. Moreover, the SS values were significantly increased in patients with high-grade EV, confirming that portal flow is directly affecting SWE values.

Ford et al [34] measured SS in patients with chronic hepatitis C virus–related cirrhosis and concluded that they were more accurate than the other parameters. However, patients with different aetiologies of CLD included in our study have showed no significant difference in mean SS, reflecting that SWE technique may be clinically applicable regardless of the etiology of CLD.

The sensitivity and specificity of SS in detecting high-risk groups of EV in this study were higher than previously found in a systematic review (95% vs 78% and 90% vs 76% respectively) [35]. Therefore, considering the excellent accuracy of SS using SWE in detecting EV with good sensitivity and specificity, we think that our results could have important clinical implication by differentiating between low and high-risk groups of EV in addition to the ability to rule out EV (high NPV) so that avoiding unnecessary endoscopy and subsequently decreasing the burden on patients, because HVPG and OGD are invasive and not accepted easily by patients, with continuous need for non-invasive tests to assess EV[36].

This study is not without limitations. First is the relatively small sample size, however, the results are preliminary and future studies with a larger sample will be more helpful. Results of the current study cannot be generalized on all patients because those with comorbidities, were excluded, hence, conducting similar research on such patients in future is suggested. Interobserver variation was not assessed in this study, although it was not the main aim, dedicated studies to address both interobserver and intra-observe variation may be required.

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CONCLUSIONS

The SS is significantly higher in a patient with CLD compared to healthy volunteers. SS values were not affected by age, gender nor aetiology of CLD. Among patients with CLD, SS values increase with increasing grade of EV. The optimal cut-off value of SS to differentiate normal from diseased liver was 12.5 KPa while the cut-off value to differentiate low-risk from high-risk groups of EV was 15.49 KPa. Compared with splenic size and platelet counts, SS had the highest accuracy in predicting high-risk groups of EV in patients with CLD, so that SWE can be a reliable and noninvasive option for monitoring EV in CLD patients and may consequently reduce the rate of unnecessary endoscopies. A future study addressing SS as an adjuvant with liver stiffness in predicting the presence of EV in CLD seems clinically useful.

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