Study of Liver and Spleen Stiffness in Hepatitis C Related Cirrhotic Patients for Predicting Esophageal Varices in Egypt

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Abstract: Background: Liver cirrhosis is a consequence of almost all progressive chronic liver diseases, approximately 10% - 20% of patients with chronic hepatitis C virus (HCV) infection have cirrhosis at first clinical presentation and as many as 20% - 30% of those who don't have cirrhosis will eventually develop this condition and its complications within one or more decades. It is estimated that HCV infects chronically about 160 million people worldwide. Between 15 and 56% of these chronic carriers will evolve towards liver cirrhosis during their lifetimes. Liver cirrhosis is a major health problem; it represents the final common pathway for wide variety of chronic liver diseases. Egypt has a very high prevalence of HCV and a high morbidity and mortality from chronic liver disease. **Aim of the Work:** It is aimed to study the use of the utility of Liver Stiffness (LS) and Spleen Stiffness (SS) in evaluating hepatitis C related cirrhotic patients compared to other non-invasive tests to predict esophageal varices (EVs) in Egypt. **Subjects:** ***Patients:*** The study was performed on 30 patients (their mean age 50.90 ± 6.82 years old, with range between 36 and 60 years), having liver cirrhosis due to chronic hepatitis C (CHC). **Controls:** 10 healthy subjects (their mean age 43.10 ± 7.20 years, with range between 33 and 53 years old). **Methods:** All subjects participated in the study were subjected to the following: Detailed history taking and complete physical examination, laboratory investigations including; CBC, AST, ALT, bilirubin, albumin, PT, INR, serum creatinine and blood urea**,** Platelet count to spleen diameter ratio**, HCV-ab,** ultrasound abdomen**,** upper GIT endoscopy, LS and SS measured by using fibroscan and Child-Pugh classification**.** All subjects were selected from the Internal Medicine department, at Bab-El Shaaryia Hospital Al-Azhar University. The study was performed in the period between July-2014 to June-2018. The nature of the study was explained to all participants and written consent was obtained. **Results:** There is significant increase in LS and SS among patients compared with controls, The mean LS among patients was; 30.98 ± 14.30 KPa and among controls was; 3.69 ± 0.75 KPa (P = 0.00) and The mean SS among patients was; 59.87 ± 12.18 KPa and in controls was; 23 ± 8.04 KPa (P = 0.00), moreover, the greater the degree of increase in LS and SS; the greater the degree of cirrhosis and EVs. Also, the greater the degree of cirrhosis, the greater the decrease of platelet count to spleen diameter ratio, The mean platelet count to spleen diameter ratio among patients was; 1.15 ± 1.17 and among controls was 2.56 ± 0.44 (P = 0.001). There is a significant decrease in platelet count and serum albumin in patients compared with controls, moreover, the greater the degree of increase in LS and SS, the greater the degree of decrease in platelet count and serum albumin. There is a significant increase of PT among patients compared with controls. There is a significant increase of ALT, AST in patients compared with controls, moreover, the greater the degree of increase in LS and SS, the greater the degree of increase in ALT and AST, in addition, the greater the degree of increase in LS and SS; the greater the degree of increase in serum bilirubin. **Conclusion:** LS and SS were increased among CHC cirrhotic patients, *in addition*, the greater the degree of LS and SS, the greater the degree of cirrhosis. LS and SS might predict EVs and the greater the degree of LS and SS, the greater the degree of EVs.

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1. Introduction

Liver cirrhosis is a consequence of almost all progressive chronic liver diseases, approximately 10% - 20% of patients with chronic hepatitis C virus (HCV) infection have cirrhosis at first clinical presentation and as many as 20% - 30% of those who don't have cirrhosis will eventually develop this condition and its complications within one or more decades. It is estimated that HCV infects chronically about 160 million people worldwide. Between 15 and 56% of these chronic carriers will evolve towards liver cirrhosis during their lifetimes. Liver cirrhosis is a major health problem**;** it represents the final common pathway for wide variety of chronic liver

diseases. Egypt has a very high prevalence of HCV and a high morbidity and mortality from chronic liver disease [1].

The presence of liver cirrhosis has prognostic relevance as it entails a relatively high risk of developing decompensation *(e.g., ascites, encephalopathy, jaundice, esophageal variceal bleeding)* or evolution toward hepatocellular carcinoma (HCC). *Also*, in the presence of liver cirrhosis current guidelines recommend periodical screening for the presence of esophageal varices (EVs) and HCC. Non-invasive methods are needed to identify clinically significant EVs. *However*, these tests had shown varying sensitivity and specificity for predicting EVs [2].

Classification of EVs according to ***Japanese society for portal HTN and EVs*** [3]**:**

- **Grade F1:** Small straight minimally elevated veins above the esophageal mucosal surface**.**
- **Grade F2:** Enlarged tortuous occupying **< 1/3** of the esophageal lumen**.**
- **Grade F3:** Large coiled-shaped**,** occupying **> 1/3** of the oesophageal lumen**.**
- **Grade F0:** Complete eradication after treatment**.**

With the exception of the most advanced stages, the diagnosis of liver cirrhosis is obtained by performing a percutaneous liver biopsy, which is an invasive technique and therefore is associated with a low but non-negligible rate of complications and even death. *Finally*, it has a non-null rate of false negative for the diagnosis of liver cirrhosis when compared with surgical biopsy. For these reasons several authors have devised non-invasive scores to predict cirrhosis using different means. The most useful are based on liver stiffness *(fibroscan),* on a panel of blood tests and on routinely available parameters [4].

Splenomegaly is a common finding in liver cirrhosis that should determine changes in the spleen's density because of portal and splenic congestion and/or because of tissue hyperplasia and fibrosis [5].

These changes can be quantified by **TE**. *However,* the role of spleen stiffness among the spleen changes associated with portal hypertension has not been fully elucidated. *Moreover*, in Egypt, liver and spleen stiffness still needs more clarification especially in predicting EVs [5].

Aim of the Work:

The aim of this study is to use the utility of liver and spleen stiffness in evaluating CHC related cirrhotic patients compared to other non-invasive tests to predict EVs in Egypt.

2. Subjects and Methods

(I) Subjects:

(a) Patients: The study was performed on 30 patients (their mean age 50.90 ± 6.82 years old, with range between 36 and 60 years), having liver cirrhosis due to CHC.

(b) Controls: 10 healthy subjects (their mean age 43.10 ± 7.20 years, with range between 33 and 53 years old).

(II) Place and duration of the study:

All subjects participated in this study were selected from the Internal Medicine department, at Bab-El Shaaryia Hospital Al-Azhar University. The study was performed in the period between July-2014 to June-2018.

(III) Ethical consideration: The nature of the study was explained to all participants and written consent was obtained.

All subjects participated in the study were subjected to the following:

[1] Detailed history taking including.

[2] Complete physical examination.

[3] Laboratory investigations including: CBC (Hb, WBCs, platelets), AST, ALT, PT, INR, albumin, bilirubin, creatinine, blood urea and HCV-Ab.

[4] Child-Pugh classification:

Table (1): Child-Pugh classification:

Measure	1 point	2 points	3 points
Total bilirubin (mg/dl)	< 2	2 - 3	> 3
Serum albumin (g/dl)	> 3.5	2.8 - 3.5	< 2.8
INR	< 1.7	1.71- 2.30	> 2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Table (2): Child-Pugh interpretation:

Points	Class	One year survival	Two year survival
5 - 6	**A**	100%	85%
7 - 9	**B**	81%	57%
10 - 15	**C**	45%	35%

[5] Platelet count to spleen diameter ratio.
[6] Upper GI endoscopy screening for EVs *(for patients only)*.
[7] Fibro-Scan for liver and spleen using Echosense fibro-Scan 502 machines.
[5] Statistical analysis:

Analysis of data was done by IBM computer using SPSS (statistical program for social science version 12) as follows: Description of quantitative variables as *mean ± SD and range,* description of qualitative variables as *number and percentage, chi-square test* was used to compare qualitative variables between groups, *unpaired t-test* was used to compare quantitative variable between both groups. *Correlation co-efficient test* was used to rank different variables against each other positively or inversely. Insignificant: if P- value > 0.05, Significant: if P-value ≤ 0.05, highly significant: if P -value ≤ 0.001.

3. Results

Table (3): Age and sex results of the studied patients:

		Control group	Patients group	t	P
		No.= 10	No.= 30		
Sex	Female	6 (60.0%)	18 (60.0%)	0.000	1.000
	Male	4 (40.0%)	12 (40.0%)		
Age	M ± SD	43.10 ± 7.20	50.90 ± 6.82	- 3.089	0.004*
	Range	33 - 53	36 – 60		

There is a significant difference between patients and controls with regard to the age (i.e. patients were older than controls).

Table (4): Comparison between controls and patients regarding some parameters:

		Control group	Patients group	t	P
		No.= 10	No.= 30		
LS (KPa)	M ± SD	3.69 ± 0.75	30.98 ± 14.30	-5.981•	0.000
	Range	3 – 5.5	5.9 – 75		
SS (KPa)	M ± SD	23.30 ± 8.04	59.87 ± 12.18	-8.832•	0.000
	Range	10 – 35	23 – 75		
Spleen diameter (mm)	M ± SD	120.40 ± 3.50	136.29 ± 28.38	-1.752•	0.088
	Range	115 – 125	13.8 – 200		
Plat (count/mm^3)*10^3/spleen diameter (mm)	M ± SD	2.56 ± 0.44	1.15 ± 1.17	3.712•	0.001
	Range	1.85 – 3.3	0.39 – 7.03		

There is a significant increase in liver and spleen stiffness in patients compared to controls with decrease in platelet count to spleen diameter ratio in patient group compared with control group.

Table (5): ROC curve for LS, SS, Plat/Spleen diameter ratio and Spleen diameter: in differentiation between patients and controls.

Parameter	Cut-off point	AUC	Sensitivity	Specificity	PPV	NPV
LS (KPa)	> 5.5*	1.000	100.00	100.00	100.0	100.0
Plat. (count/mm^3)*10^3/spleen diameter (mm)	≤1.82*	0.967	96.67	100.00	100.0	90.9
Spleen diameter (mm)	> 125*	0.883	86.67	100.00	100.0	71.4
SS (KPa)	> 35*	0.980	96.67	100.00	100.0	90.9

Table (6): comparison between upper GI endoscopy result with some parameters in patient group**:**

		No EVs	EVs	t	P
		No.= 8	No.= 22		
LS (KPa)	M ± SD	15.59 ± 4.31	36.57 ± 12.37	-4.651	0.000
	Range	5.9 – 18.7	20 – 75		
SS (KPa)	M ± SD	44.13 ± 9.23	65.59± 6.91	-6.878	0.000
	Range	23 – 54	53 – 75		
Spleen diameter (mm)	M ± SD	137.25 ± 6.67	135.95 ± 33.11	0.109	0.914
	Range	130 – 148	13.8 – 200		
Plat. (count/mm^3)*10^3/spleen diameter (mm)	M ± SD	1.34 ± 0.40	1.08 ± 1.34	0.535	0.597
	Range	0.91 – 1.82	0.39 – 7.03		

There is a significant increase in liver and spleen stiffness in patients with positive upper GI endoscopy compared to patients with negative upper GI endoscopy; also, there is a significant decrease in platelet count to spleen diameter ratio in patients with positive upper GI endoscopy compared to those with negative upper GI endoscopy.

Table (7): Sensitivity and specificity of liver stiffness, spleen stiffness, spleen diameter and platelet count to spleen diameter ratio in patient and control groups.

Parameter	Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
LS (KPa)	>5.5 *	1.000	100.00	100.00	100.0	100.0
Plat. (count/mm^3)*10^3/spleen diameter (mm)	≤1.82 *	0.967	96.67	100.00	100.0	90.9
Spleen diam (mm)	>125 *	0.883	86.67	100.00	100.0	71.4
SS (KPa)	>35 *	0.980	96.67	100.00	100.0	90.9

LS, SS and platelet count to spleen diameter ratio are highly sensitive and specific for predicting fibrosis in patients compared to controls.

Table (8): Sensitivity and specificity of liver and spleen stiffness for diagnosing EVs in patient group:

Parameter	Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
LS (KPa)	>18.7 *	1.000	100.00	100.00	100.0	100.0
SS (KPa)	>48 *	0.983	100.00	87.50	95.7	100.0

The cut off point for detection of esophageal varices was **>18.7 (KPa)** for liver stiffness and **>48 (KPa)** for spleen stiffness.

Table (9): Relationship between liver and spleen stiffness with various degrees of esophageal varices:

		Grade II	Grade III	t	p
		No. = 6	No. = 16		
LS (KPa)	**M ± SD**	27.00 ± 4.60	38.37 ± 10.64	8.571	0.002
	Range	20 – 33	27 – 75		
SS (KPa)	**M± SD**	60.50 ± 7.56	67.00 ± 5.63	3.566	0.048
	Range	53 – 71	53 – 75		

There is progressive increase in liver and spleen stiffness with increased degrees of esophageal varices.

4. Discussion

Hepatitis C virus (HCV) is a hepato-tropic RNA virus that causes progressive liver damage, which might result in liver cirrhosis and HCC. Globally, between 64 and 103 million people are chronically infected [(6)].

It is estimated that HCV infects chronically about 160 million people worldwide. Between 15 and 56% of these chronic carriers will evolve towards liver cirrhosis during their lifetimes [(1)].

The presence of liver cirrhosis has prognostic relevance as it entails a relatively high risk of developing decompensation *(e.g. Ascites, encephalopathy, jaundice, esophageal variceal bleeding)* or evolution toward HCC.

Also, in the presence of liver cirrhosis current guidelines recommend periodical screening for the presence of EVs and HCC [(5)].

Variceal veins in the esophageal and gastric submucosa are part of the portosystemic channels which develop when pressure increases in the portal venous bed**.** In these sites**,** varices may rupture and bleed, irrespective of the cause of portal hypertension**.** They are the most common collateral pathway being present in 80-90% of portal hypertensive patients [(7)].

Liver biopsy is considered reference standard for diagnosing severe and advanced hepatic fibrosis in people with CHC, who are expected to have higher benefit from treatment [(8)].

Due to the limitations of liver biopsy, non-invasive alternatives including Fibro-Scan (TE) have been developed. TE is an easy and quick clinical non-invasive method to perform and it could be useful to evaluate liver fibrosis as to monitor liver disease progression [(9)].

Studies employing different technical approaches have highlighted the potential utility of SS assessment for the prediction of the presence of EVs and the degree of portal HTN in cirrhotic patients [(5)].

The obtained results of current study showed that: 30 patients (12 males and 18 females), have mean age of 50.90 ± 6.82 years old (ranged between 36 and 60 years) and control group consisted of 10 subjects (4 males and 6 females), have mean age of 43.10 ± 7.20 years old (ranged between 33 and 53 years) (table 3).

LS among patients was; 30.98 ± 14.30 KPa and among controls was; 3.69 ± 0.75 KPa, this result showed a highly significant increase in mean LS of patients compared with controls (P = 0.0000) (table 4).

LS at the level of 5.5 KPa (cut-off point) is highly sensitive for detection of patients more than this point as well as highly specific for normal subjects (100 % for both) (table 5).

LS among patients with EVs was; 36.57 ± 12.37 KPa and among patients without EVs was; 15.59 ± 4.31 KPa, this results showed a highly significant increase in mean LS among patients with EVs compared with patients without EVs (P = 0.0000) (table 6).

SS among patients was; 59.87 ± 12.18 KPa and in controls was; 23 ± 8.04, this result showed a highly significant increase in mean SS among patients compared with controls (P = 0.0000) (table 4).

SS among patients with EVs was; 65.59± 6.91 KPa and among patients without EVs was; 44.13 ± 9.23 KPa, this result showed significant increase in mean SS among patients with EVs compared with patients without EVs (P = 0.0000) (table 6).

LS among patients with grade II EVs was; 27.00 ± 4.60 and among patients with grade III EVs was; 38.37 ± 10.64. Also, The mean SS among patients with grade II EVs was; 60.50 ± 7.56 and among patients with grade III EVs was; 67.00 ± 5.63. These results showed significant increase in LS and SS with increasing degrees of EVs (table 9).

Also, the results showed that LS at the level of 18.7 KPa (cut-off point) is highly sensitive for detection of patients with EVs. *In addition*, it is highly specific for detection of patients without EVs (100%for both). *Similarly*, SS at the level of 48 KPa (cut-off point) is highly sensitive (96.67) for detection of patients with EVs. *Moreover*, it is highly specific (100%) for detection of patient without EVs (table 8).

These results were in agreement with those reported by ***Chon et al.*** [10], who found that TE values were selected as independent predictor of EVs development and patients with a TE value >19 kPa were at significantly greater risk than those with a TE value ≤ 19 kPa and in agreement with those reported by ***Kazemi et al.*** [11], who found that Liver stiffness measurement value <19 kPa was highly predictive of the absence of esophageal varices grade ≥ II (Se: 84%, PPV: 47%, NPV: 93%).

Also, these results were in agreement with those reported by ***Robic et al.*** [12], who found that within the two-year follow-up, 41 patients developed, at least, one liver disease related complication. The performances of HVPG and LS for predicting the occurrence of these complications were not significantly different: AUROC 0.815 [0.727–0.903] and 0.837 [0.754–0.920], respectively. When considering only complications related to portal HTN, both methods were found to be similarly accurate: AUROC 0.830 [0.751–0.910] and 0.845 [0.767–0.823], for HVPG and LS, respectively. When patients were divided in two groups according to a LS value below or above 21.1 kPa, actuarial rates of remaining free of any complication at 2 years were 85.4% *vs.* 29.5%, respectively. When only PHT related complications were considered, these rates were 100% *vs.* 47.5%, respectively. The performances of LS and HVPG were also similar in the subgroup of 65 patients with cirrhosis.

Also, the obtained results in the current study revealed that, Platelet count to spleen diameter ratio have a significant positive correlation with advancing fibrotic stage (1.15 ± 1.17) (P = 0.001) (table 4). This means that, the greater the decrease in the degree of Platelet count to spleen diameter ratio, the greater the degree of liver fibrosis.

Also, the obtained results in this study, revealed that, LS have significant positive correlation with SS, Total bilirubin, this means that as the Total bilirubin increases, LS and SS increases.

The obtained results in this study *similarly*, revealed that, LS have significant negative correlation with Platelet count and Platelet count to spleen diameter ratio, Albumin and PT concentration, this means that as the Platelet count, Platelet count to spleen diameter ratio, Albumin and PT concentration decreases, LS increases.

The obtained results in this study *similarly*, revealed that, SS have significant negative correlation with Platelet count and Platelet count to spleen diameter ratio, Albumin and PT concentration, this means that as the Platelet count, Platelet count to spleen diameter ratio, Albumin and PT concentration decreases, SS increases.

The obtained results of our study were in agreement with those reported by ***Stefanescu et al.*** [13] who found that Spleen stiffness showed higher values in liver cirrhosis patients as compared with chronic hepatitis and with controls: 60.96 *vs* 34.49 *vs* 22.01 KPa (P <0.0001). In the case of liver cirrhosis, spleen stiffness was significantly higher in patients with varices as compared with those without (63.69 *vs* 47.78 KPa, P <0.0001), 52.5 KPa being the best cut-off value, with an area under the receiver operating characteristic of 0.74. Using both liver and spleen

stiffness measurement we correctly predicted the presence of esophageal varices with 89.95% diagnostic accuracy and those reported by ***Sharma et al.*** [5] who found that LS ≥27.3 kPa had an Se of 91%, Sp of 72%, positive predictive value (PPV) of 89%, negative predictive value (NPV) of 76%, and a diagnostic accuracy of 86% in predicting EV. LSPS ≥3.09 had Se and Sp of 89% and 76%, respectively, and a PSR cut-off value of 909 or less had Se of 64%, Sp of 76%, and diagnostic accuracy of 68% in predicting EV. SS ≥40.8 kPa had Se (94%), Sp (76%), PPV (91%), NPV (84%), and diagnostic accuracy of 86% for predicting EV. SS was significantly higher in patients who had large varices (56 vs. 49 kPa, *P*=0.001) and variceal bleed (58 vs. 50.2 kPa, *P*=0.001). Combining LS+SS (27.3+40.8 kPa) had Se of 90%, Sp 90%, PPV 96%, NPV 79%, and a diagnostic accuracy of 90%. HVPG (*n*=52) showed significant correlation with SS (*r*=0.433, *P*=0.001), LSPS (*r*=0.335, *P*=0.01), and PSR (*r*=−0.270, *P*=0.05), but not with LS (*r*=0.178, *P*=0.20).

The possible explanations for the above significant correlations may be explained by several pathogenic factors: The portal HTN is initiated by the increased vascular resistance to portal blood flow and is primarily caused by structural changes such as fibrotic scar tissue and regenerative nodules compressing portal and central venules. Furthermore, previous reports showed that swelling of hepatocytes and capillarisation of hepatic sinusoids (loss of endothelial fenestrations and collagen deposition in the space of Disse) are part of the increased vascular resistance. The increase in the portal vein blood flow occurs in a more advanced stage of portal hypertension and contributes to its maintenance and aggravation [14].

Liver fibrosis is a dynamic process in which activated hepatic stellate cells are involved in the synthesis of matrix proteins and the regulation of matrix degradation. Fibrosis stage is a result of the imbalance between synthesis and degradation of extra-cellular component. In advanced stages, the liver contains approximately 6 times more (ECM) extracellular matrix than normal, including collagens (I, III, and IV), fibronectin, undulin, elastin, laminin, hyaluronan, and proteoglycans. Accumulation of ECM results from both increased synthesis and decreased degradation [15].

Normally deposition of the ECM is a dynamic and reversible process mediated by several specific matrix metallo-proteinases (MMPs), which in turn are regulated by soluble inhibitors termed TIMPs (tissue inhibitor of metalloproteinase). A number of serum markers for ECM deposition and removal have been evaluated as candidate markers for liver fibrosis, and a small number of studies have evaluated their usefulness in predicting esophageal varices. Potential markers examined to date include the glycoproteins, hyaluronic acid and laminin, and numbers of the collagen family including procollagen III and type IV collagen. Esophageal collaterals develop as a consequence of portal hypertension, being formed by vascular remodeling and angiogenesis [16].

Key molecules though to be involved in this process include nitric oxide and vascular endothelial growth factor (VEGF). Serum nitrate levels could predict the large esophageal varices [17].

To achieve more high accuracy, ***Kim et al.*** [18] recently proposed a novel prediction model liver stiffness-spleen diameter to platelet ratio score [LSPS]) using TE values and other parameters that reflect portal hypertension as constituent variables in patients with CHB. Overall, this model had excellent diagnostic accuracy for prediction of high risk esophageal varices (HEV, AUROC=0.953; negative predictive value 94.7%, positive predictive value 93.3%). Beyond this cross-sectional analysis, a subsequent study by same group recently reported that LSPS can be a reliable predictor of the development of variceal bleeding. In this prospective, longitudinal study of 577 patients with CHB, those with LSPS ≥5.5 had higher cumulative incidence rates of esophageal variceal bleeding during the follow-up period and LSPS score ≥6.5 was an independent risk factor of variceal bleeding from HEV, indicating that prophylactic treatment should be considered in these high risk patients.

Conclusion:

LS and SS were increased among CHC cirrhotic patients, *in addition*, the greater the degree of LS and SS, the greater the degree of cirrhosis. LS and SS might predict EVs and the greater the degree of LS and SS, the greater the degree of EVs.

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