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Original Research Article

Comparison of Liver and Splenic Stiffness for the Prediction of Esophageal Varices in Chronic Liver Disease Patients Attending a Tertiary Care Centre

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Abstract:

Introduction: Chronic liver disease (CLD) cases progesses to esophageal varices (EV) as the most common complication. EV is detected by esophagogastroduodenoscopy (EGD), which causes financial burden and side effects to the patients. Till date, liver stiffness (LS) & spleen stiffness (SS) are the mainly explored non-invasive tools by the researchers. So our study aimed to compare efficacy of LS and SS as non-invasive tools to predict EV.

Material and methods: The current research was a cross sectional & comparative hospital based done on CLD patients visiting Dispur Hospitals Pvt Ltd, Guwahati, Assam. All patients underwent upper endoscopy & then furthermore assessed for liver stiffness (LS) & spleen stiffness (SS) with Acoustic Radiation Force Impulse (ARFI) elastography. Valid ARFI measurements could be seen only in 138 patients. To compare LS and SS values, 'Wilcoxon signed-rank test,' 'Mann-Whitney U test', 'Spearman correlation coefficient' were applied and their 'receiver operating characteristics (ROC) curves' were compared using the 'DeLong test' and "p value <0.05 was considered as significant."

Result: The study recruited 140 CLD cases with male preponderance and mean age of 48.6±12.4years. The main sign & symptom seen in patients was fatigue trailed by loss of appetite and the chief etiology of CLD was alcohol followed by hepatitis B. Mean liver stiffness & SS values were significant in EV and a significant linear correlation of them with grade of EV was seen. AUROC analysis of LS and SS depicted relatively better non-significant predictive value of SS than LS. SS had better sensitivity than LS whereas LS had slightly better specificity than SS.

Conclusion: The current study found SS to be good predictor of EV than LS although it was not significant. Therefore we suggest, both LS and SS combined as a helpful non-invasive tool in predicting high risk EV as both have good specificity & sensitivity and can be easily performed in single sitting.

Keywords: CLD, EV, Liver stiffness, Splenic stiffness etc.

Introduction

Chronic liver disease (CLD) comprises slow damage destruction and restoration of liver parenchyma ultimately causing fibrosis & cirrhosis leading to alteration of functions by liver. CLD represents a critical public health issue with 4.5-9 percent occurrence around the globe. [1] CLD is a chief contributory factor responsible for mortality with many complications growing the severity of the disease. The most common complication seen in around 50 percent of the CLD patients is esophageal varices (EV) and the haemorrhage of EV is a serious issue that happens in 25-40 percent of the cirrhosis patients with mortality rate of 20%. [2] If a patient suffers from an acute haemorrhage of EV then the patient develops 70% raised risk of having bleeding episode again within the same year. The management of CLD depends on its stage and the grade of EV often depicts the severity of the disease. So it is significant to detect EV in the CLD patients and esophagogastroduodenoscopy (EGD) is the gold standard procedure to screen EV. The current guidelines recommended all newly diagnosed cirrhosis patients to go through EGD to spot presence of EV. [3] However, EGD is a costly & invasive technique with other associated complications of sedation so it is preferred to be done only in high-risk patients. Hence substantial concern exists to develop non-invasive tools to

select high-risk patients with EV. Previous studies have documented several serum & radiological analysis to predict EV such as "serum fibrosis markers, liver stiffness (LS), spleen stiffness (SS), LS-spleen diameter to platelet ratio score". [4] Out of all the above non-invasive parameters, both liver & spleen stiffness has been reported to be more accurate in predicting EV. Previous studies have assessed LS and SS by Transient elastography (TE) but due to few drawbacks of TE, [5] now clinicians opt for Acoustic radiation force impulse (ARFI) to estimate tissue stiffness. [6-8] numerous scientsts have exposed that assessment of LS by elastography can be helpful to spot EV especially along with other non-invasive methods. Recent guidelines suggest to circumvent EGD in cases having "LS <20kPa & platelet count >150,000". [9] Hence it is believed that LS signifies the degree & existence of EV in CLD. However few sientists state the opposite to this. So due to inconsistent and insufficient diagnostic accuracy of the results, the role of LS only in identifying EV is controversial. [3]

In past years, research has put stress on assessment of SS to spot EV. Progression and associated complication of CLD causes spleen congestion & fibrosis, leading to increase in its stiffness. In recent times, many researchers have tried to elucidate the efficacy of splenic stiffness & LS to identify EV in CLD csases, although till now the results have been inconclusive. Few studies documented evaluation of SS by elastography to be more accurate & effective in identifying and predicting grade of EV compared to LS. Conversely, few studies concluded liver elastography to be better than spleen elastography as they found variable SS results which were highly unreliable to predict EV. [10,11] So the analytic value of SS compared to LS in identifying EV in CLD patients is still doubtful. Hence in view of the indecisive efficacy of 'splenic stiffness' & 'liver stiffness' in EV prediction, we aimed a study to evaluate & compare the analytic efficacy of splenic and liver stiffness to identify and predict the grade of EV in CLD patients.

Material and Method

The current research was a cross sectional & comparative hospital based research done on CLD patients visiting Dispur Hospitals Pvt Ltd, Guwahati, Assam by the Department of Radio-diagnosis in association with Department of Gastroenterology for around 1 year i.e. from September 2018 to September 2019. 140 CLD patients of both sexes with age >18years were recruited for the study after taking approval from ethics committee. Patients were enrolled in the study after obtaining written informed consent from them and consecutive sampling technique was used. Clinically CLD diagnosed patients with radiological, biochemical, serological and histopathological parameters suggestive of the disease were enrolled for the research. Pregnant CLD females and CLD cases with portal hypertension (PH) due to extra or post hepatic reason, cases with inconclusive elastographic evaluation and patients not fit for endoscopy were excluded from the research. All subjects underwent upper endoscopy using a flexible Olympus S170 series UGI endoscope and they were further evaluated for LS and SS with ARFI by an Acuson S2000 ultrasound system equipped with a convex transducer. When ARFI was done, out of 140 patients, valid values could be taken in only 138 patients. Firstly, liver was scanned trailed by spleen scanning in every patient. An 'ARFI elastography' values was assesed at the time of breath hold to lessen motion during respiration. 'Standard B-mode' sonographic scan was done to evaluate the ascites existence.

LS and SS dimensions were noted from two different locus in 'right lobe' of liver and spleen respectively in segments 7 or 8. The 'ARFI' values of right lobe are reported to be better in identifying fibrosis of liver than left lobe so right lobe of liver and spleen was assessed and the median of ten applicable values was taken for every ARFI value. For liver assessment, patients were positioned in 'supine position' with maximum abduction of right arm and to note the space from skin to liver capsule & liver size, a sagittal approach in the mid clavicular line was used. For spleen evaluation, participants were asked to uphold either supine position or 'right lateral decubitus position' with maximum abduction of left arm.

During B-mode scanning of the spleen, the position with finest visibilty of borders & angles of spleen was retained. For LS and SS measurements by using ARFI mode, region of interest (ROI) box was sited to a not more than 7cm from surface of skin, circumventing any vessels between 2-3cm below the liver or splenic capsule respectively. Whenever possible during liver and spleen evaluation, the ROI angle was kept perpendicular.

The greatest length & transverse width of spleen and mean hepatic & splenic stiffness in m/sec were recorded. The 'Wilcoxon signed-rank test' and 'Mann-Whitney U test' were assessed to compare the differences in values of mean liver and splenic stiffness according to grades of varices. The stiffness values were assessed using 'receiver operating characteristics (ROC) curves' for the detection of significant EV. 'Area under the ROC curve (AUROC)' was calculated using the 'trapezoidal rule' and compared using the 'DeLong test'. Cut-off values for LS and SS for prediction of high risk varices were analyzed using 'Youden index'. 'Spearman correlation coefficients test' was used to find correlations between different parameters. "A p value <0.05 was regarded as significant" for each test.

Result-

The study was comprised of 140 CLD patients with age >18years with mean age of 48.6±12.4years. Figure 1 shows that the present study had maximum number of males i.e. 129(92.00%) than the females i.e. 11(8.00%). Table 1 depicts the grouping of patients based on their age i.e. age group 30-40, 41-50, 51-60, 61-70 and 71-80years with 16(11.00%), 38(27.00%), 52(37.00%), 32(22.00%) and 2(1.40%) patients respectively. CLD patients enrolled in current study had varying etiology i.e. alcohol, hepatitis B, hepatitis C, NAFLD/cryptogenic and autoimmune with 90(64.28%), 24(17.10%), 8(5.70%), 16(11.40%) and 2(1.40%) patients consecutively.

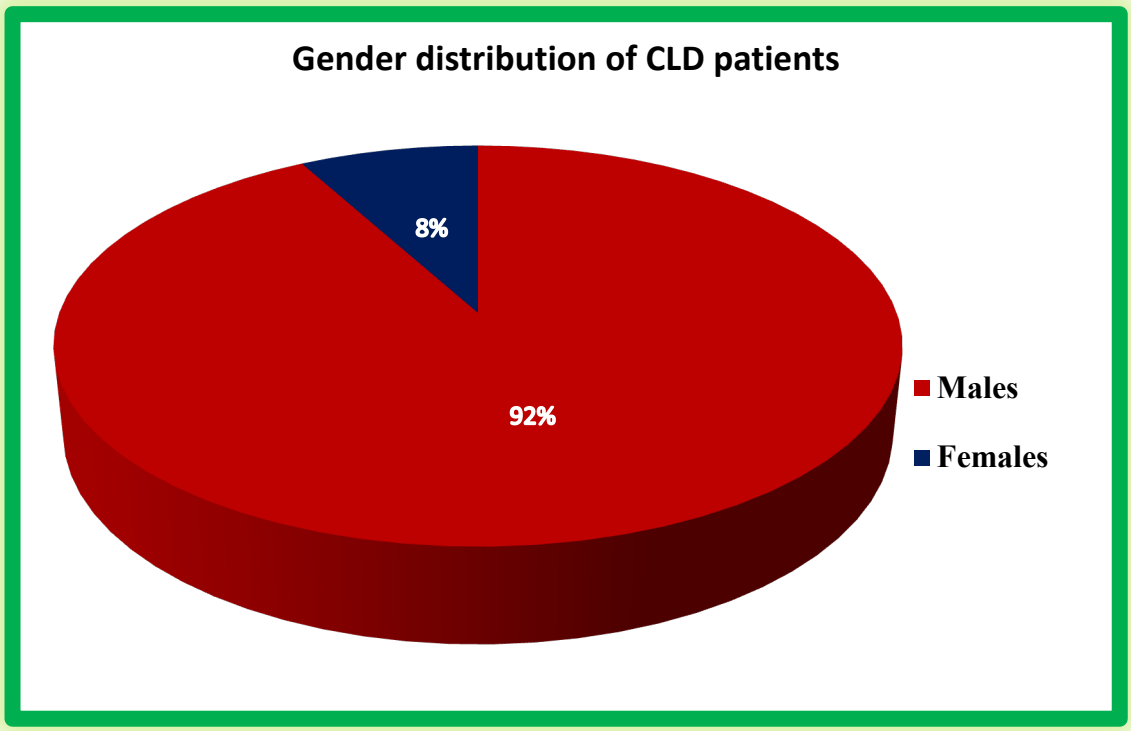

Figure 1: Gender distribution of CLD patients

Table 1: Distribution of patients based on demographic variables

Variable		No. of patients n (%)
Age in years	30-40	16(11.00%)
	41-50	38(27.00%)
	51-60	52(37.00%)
	61-70	32(22.00%)
	71-80	2(1.40%)
Etiology	Alcohol	90(64.28%)
	Hepatitis B	24(17.10%)
	Hepatitis C	8(5.70%)
	NAFLD/Cryptogenic	16(11.40%)
	Autoimmune	2(1.40%)

Figure 2 clearly illustrates the sign and symptoms revealed by CLD patients. Main communal symptom was fatigue found in all 140 cases (100.00%), followed by loss of appetite i.e.138 patients (98.57%) and weight loss i.e. 136 patients (97.14%),. Other symptoms were ascites, jaundice, muscle loss, oedema, abdominal distension, spider-like veins, itching and bruising with 128(91.14%), 122(87.14%), 90(64.42%), 60(42.85%) and 59(42.14%), 55(39.28%), 50(35.71%) and 40(28.57%), patients respectively.

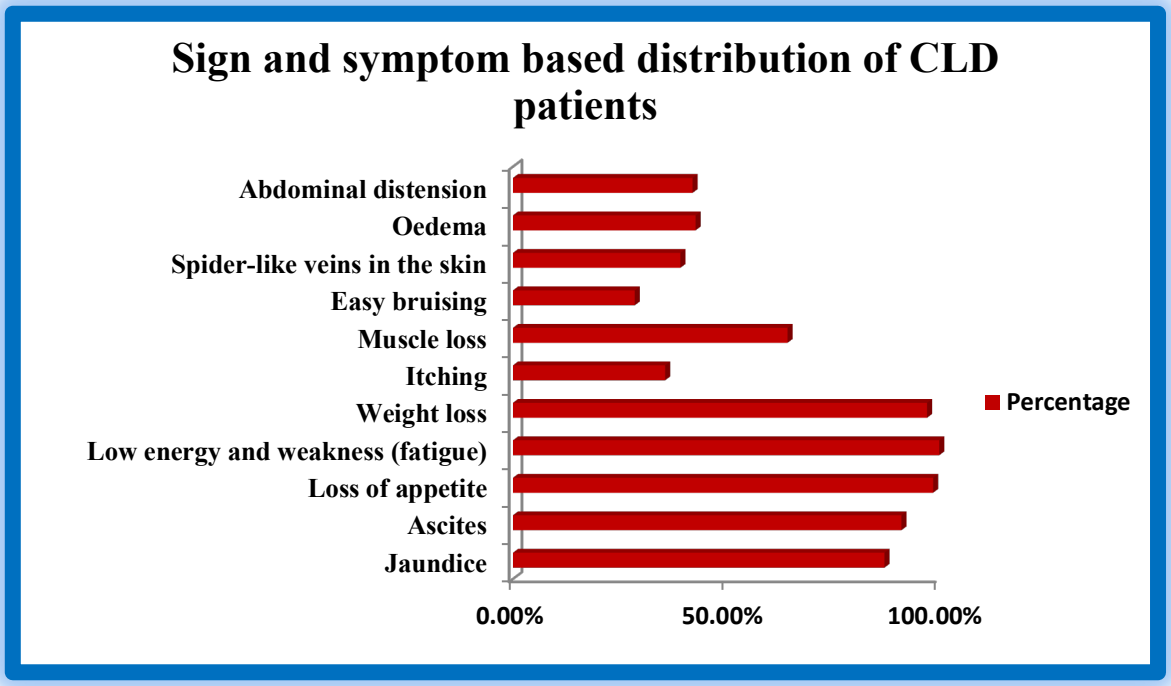

Figure 2: Sign and symptom based distribution of CLD patients

When ARFI was done, out of 140 patients, valid values could be taken in only 138 patients (98.5%). When patients underwent endoscopy, it was observed that, maximum patients i.e. 73(52.89%) had large varices (>5mm) regarded as positive result and 65(47.10%) had small varices with RCS regarded as negative result as clearly visible in Table 2.

Table 2: Findings in Upper GI endoscopy

Grade of esophageal varices	No. of patients n (%)
Large varices (>5mm) – Positive result	73 (52.89%)
Small varices with RCS- Negative result	65 (47.10%)

***Large varices taken as positive & small as negative results**

Table 3 depicts the mean values of LS and SS in CLD patients with large and small EV. Mean LS was increased significantly in high risk cases with large varices (>5mm) i.e. 3.0600±.58 compared to small varices with RCS patients i.e. 2.7712±0 .46. A significant linear correlation (Spearmanρ= 0.374, 'P<0.01') was observed among LS and high risk EV, stating that LS increases parallely with the increase in grade of EV. Mean SS was also increased significantly in high risk cases with large varices (>5mm) i.e. 3.3067±.19 than patients with small varices i.e. 3.0591±0.19.

Table 3 clearly states that a significant linear correlation (Spearmanρ =0.527, p<0.01) exists between SS and high risk EV i.e. with increase in SS, parallel increase in grade of EV was seen.

Table 3: Showing mean liver and splenic stiffness in high Risk esophageal varices

Parameters	Large varices (>5mm)	Small Varices with RCS	p-value
Liver stiffness in m/sec (Mean±SD)	3.0600±0 .58	2.7712±0 .46	<0.01
Splenic stiffness in m/sec (Mean±SD)	3.3067±0 .19	3.0591±0.19	<0.01

Figure 3 and table 4 compares diagnostic ability & accuracy of liver & splenic stiffness as predictor of EV in CLD cases. 'AUROC analysis' showed that SS values by 'ARFI' had relatively better predictive values for high risk EV i.e. 0.804 than LS with AUROC of 0.716 but no significant difference could be demonstrated between LS & SS for predicting high risk EV. 'ROC curves' were compared using 'DeLong test'. For SS, specificity was found to be 83.1% and sensitivity was 78.1% as compared to LS with specificity of 86.2% and sensitivity of 58.9% in predicting high risk EV. The best cutoff values were 3.27 m/sec for high risk varices. Both LS and SS collectively can effectively predict high risk EV which will allow better outcome in patient management.

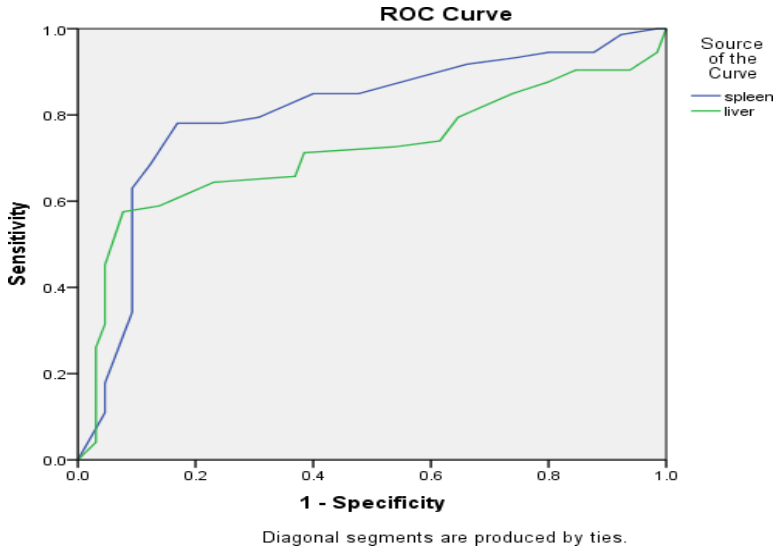

Figure 3: Showing ROC curves of liver and spleen stiffness measured by ARFI elastography for predicting the presence of high risk EV

Table 4: Showing comparison of AUC of liver and spleen stiffness

Parameter	AUC	Standard Error	Difference	p-value
Liver stiffness	0.716	0.045	-0.088	0.1439
Spleen stiffness	0.804	0.040		

Discussion

The current study was done on CLD patients visiting a tertiary care hospital of Guwahati, Assam. CLD patients with advancement in the disease progress towards the major complications like EV regardless of its cause. These EV are linked with raised mortality rate up to 10 to 20 percent of the disease at 6weeks. [9] So it is vital to assess the risk & prognosis of the EV at the time of diagnosis of CLD. EGD is the standard technique to predict risk of EV although it is invasive, uncomfortable and costly. Scientists have revealed many surrogate non-invasive markers and out of them so far LS has been proved as a fine non-invasive prognostic marker by many studies. [12-15]There exists many clinical conditions when LS measurement is not viable to perform and studies have revealed that in such cases, SS signifies a dependable choice. [16] So in our study we have compared liver & splenic stiffness to identify EV in CLD subjects. The subjects of present study had mean age of 48.6±12.4years with age range of 30-80years. Majority of the cases were from the age group 51-60years (37.14%) trailed by 41-50 years (27.14%) with dominance of males. Study by Kishor Kumar B et al. [17] also found majority of patients in the similar age group. Another study by Shivam D et al. [18] is strongly in agreement as they also had mean age (42.8±14.4years) close to our result. Studies by Renata Fofiu et al. [19] and Carmen Fierbinteanu-Braticevici1 et al. [16] found much higher mean age than current study. The finding of male predominance is in conformity with Elkrief et al. [7] and AS N et al. [20] the maximum patients of present study showed the sign and symptoms of body weakness (fatigue) chased by loss of appetite. The foremost etiology behind CLD observed in patients of our study was alcohol (64.28%) follwed by hepatitis B (17.1%). This outcome is in harmony with Sarangapani A et al. and in disparity with Carmen Fierbinteanu-Braticevici1 et al. [16] and Danish M et al. [21] as they observed hepatitis C (63%) as major etiology of CLD.

In current study, majority of the cases had large varices, which is in harmony with Kishor Kumar B et al. [17] and in dissimilarity with the findings by Shivam D et al. [22] and El Lehleh et al. [23] as majority of their patients had small varices. The mean LS and SS in our study were significantly raised in large varices patients compared to small varices and a significant linear correlation between them and the high risk EV was observed. This result regarding LS is in concurrence with Shivam D et al. [22] and Horia et al. with varying cutoff values. Although Xiao-Ping Ye et al. revealed non-significant correlation among LS and grade of EV. The findings about SS of present study are in accordance with study by Attia D et al. [24], Yoshitaka takuma et al. and Kim HY et al. [5] However Okuda K et al. had findings in disagreement to ours. SS measurement in our study showed a stronger association than LS measurement with presence of EV in CLD patients. This outcome is strongly supported by Carmen Fierbinteanu-Braticevici1 et al. [16] as they also found significantly higher mean SS than LS showed a

stronger relationship with EV. In consensus to present study, Berzigotti et al. and Tag-Adeen et al. [25] also conferred that raised LS resulted in larger spleen size which leads to a more possibility of finding varices.

When AUROC of LS and SS were compared, our study depicted relatively better predictive value of SS (0.804) than LS (0.716). SS had better sensitivity (78.1%) compared to LS (58.9%), althogh specificity of both of them was almost equal (83.1% compared to 86.2%). Current study did not locate any significant statistical difference among LS and SS measurements in predicting high risk EV. This outcome is in disparity with study by Elkrief et al. [7] as they showed better sensitivity for LS (82%) compared to SS (48%) though SS had improved specificity (71%) than LS (45%). A metaanalysis by Xiaowen Ma e.t al. [26] concluded that SS to be superior than LS for identifying EV in CLD cases as they found that sensitivity and specificity for LS as 83% and 66% while for SS 88% and 78% respectively.

Study by Alsebaey et al. [27] also observed better sensitivity (93%) and specificity (84%) for SS than LS (82% & 72% respectively). On the other hand study by Rifai et al. revealed significantly improved performance of LS (AUROC 0.90) than SS (AUROC 0.68) for predicting EV. Another study by Morisaka H et al. reveals SS accuracy to be low to identify severe EV. Study by Stefanescu et al. [28] observed comparable results for LS and SS as sensitivity and specificity for LS was 89% & 56% and for SS it was 89% and 51% consecutively. The study surely showed better SS results than LS but findings were not significant. Moreover previous data regarding comparison of efficacy of liver & splenic stiffness for predicting EV is inconsistent. So undoubtedly, further research is desirable to validate the analytic value of liver & splenic stiffness in predicting EV. Hence we suggest that both LS and SS can mutually be effective in predicting high risk EV. Studies by Sharma P et al. and Stefanescu H et al. have also shown that further combining liver & splenic stiffness assessment has improved diagnostic accuracy for predicting EV.

Conclusion

CLD patients generally develop EV along with progression of disease. EV is diagnosed by EGD which causes financial burden and side effects to the patients. So it is not likely to go for EGD in every alleged patient so heath providers should be proficient to predict the risk of EV by other non-invasive tools, LS and SS being the most explored by the researchers. So our research was focussed to compare efficacy of LS and SS as non-invasive tools to predict EV. The current study found SS to be good predictor of EV than LS although it was not significant. Therefore we suggest, both LS and SS combined as a helpful non-invasive tool in predicting high risk EV as both have good specificity & sensitivity and can be easily performed in single sitting. This will avoid unnecessary monetary load and distress caused by EGD to the patients and will assist clinicians in timely diagnosis along with appropriate treatment of the EV patients.

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