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Original Research Article

To Evaluate of Liver Stiffness on Elastography Ultrasound

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Abstract: ***Introduction*****:** Liver stiffness (LS) assessed by means of Ultrasound elastography can safely replace liver biopsy in several clinical scenarios, particularly in patients with chronic viral hepatitis. However, an increase of LS may be due to some other clinical conditions not related to fibrosis, such as liver inflammation, acute hepatitis, obstructive cholestasis, liver congestion, infiltrative liver diseases. ***Material and Methods*****:** This is a prospective and observational study was conducted in Department of Radiology at a Tertiary care teaching Hospital over a period of 6 months. Inclusion criteria: Patients of either gender between age group 30 to 60 years. Elevated liver enzymes. Exclusion criteria: Biopsy samples smaller than 15 mm. Hepatic transplant patients in last 6 months. Coagulation disorders and risk of bleeding following biopsy. Patients with biopsy results did not meet the required quality criteria. ***Result*****:** In our study, the most of the patients the age group of 41-60 years i.e., 39 out of 70 (55.7%), followed by 21-40 years, i.e., 23 out of 70 (32.8%). Maximum number of patients were male 51 (72.8%) and female 19 (27.1%) in our study. The METAVIR fibrosis grades were as follows: F0-F1 = 37 (52.8%); F2 = 13 (18.5%); F3 = 9 (12.8%); F4.1 = 7 (10%); F4.2 = 4 (5.7%). Total 19 patients experienced one or more Liver-related events; the first Liver-related events were: 17 hepatic decompensations (3 variceal bleeding, 3 ascites, 5 Hepatic encephalopathy, 4 Jaundice, 1 Hepatorenal syndrome and 1 Spontaneous bacterial peritonitis), 1 hepatocellular carcinomas. ***Conclusions:*** Liver stiffness by TE accurately predicts the risk of death or hepatic complications in patients with chronic liver disease. TE may facilitate the estimation of prognosis and guide management of these patients.
Keywords: Liver stiffness, Ultrasound, Fibrosis, Hepatic complication.

INTRODUCTION

Ultrasound elastography (USE) is an imaging technology sensitive to tissue stiffness that was first described in the 1990s [1]. It has been further developed and refined in recent years to enable quantitative assessments of tissue stiffness. Electrography methods take advantage of the changed elasticity of soft tissues resulting from specific pathological or physiological processes [2]. For instance, many solid tumours are known to differ mechanically from surrounding healthy tissues. Similarly, fibrosis associated with chronic liver diseases causes the liver to become stiffer than normal tissues. Electrography methods can hence be used to differentiate affected from normal tissue for diagnostic applications [3].

Recently, non-invasive liver stiffness measurement (LSM) using transient electrography (TE) has been reported to be well correlated with histologically assessed liver fibrosis stages and has also been shown to be an accurate predictor of the development of hepatocellular carcinoma (HCC) in patients with chronic liver disease [4]. Liver stiffness correlates with cirrhosis complications including variceal haemorrhage, ascites, and hepatocellular carcinoma (HCC) [5]. Many of these complications are portal hypertension-related; indeed, liver stiffness correlates with the hepatic venous pressure gradient [6]. Although the excellent performance of TE for predicting the histological stage of liver fibrosis has been well known, TE is not available in every hospital or clinic. In addition, LSM is difficult in patients with obesity or narrow intercostal spaces and impossible in patients with ascites [7]. Therefore, the physical appearance of the liver as evaluated using ultrasonography (US) is still thought to provide

important information for the prediction of liver fibrosis. Thus, we wondered if the US findings could be a substitute for TE [8].

The objective of our study was to examine the association between liver stiffness and the risk liver-related complications among patients with diverse hepatic disorders and severities to reflect routine clinical practice. We report risk estimates at clinically relevant liver stiffness thresholds that that may help physicians estimate the prognosis of their patients and guide their management.

MATERIAL AND METHODS

This is a prospective and observational study was conducted in Department of Radiology at a Tertiary care teaching Hospital over a period of 6 months.

Inclusion criteria

- Patients of either gender between age group 30 to 60 years.
- Elevated liver enzymes.

Exclusion criteria

- Biopsy samples smaller than 15 mm
- Hepatic transplant patients in last 6 months
- Coagulation disorders and risk of bleeding following biopsy
- Patients with biopsy results did not meet the required quality criteria.

In this study, patients with impaired hepatic enzymes were subjected to biopsy and elastography to determine the severity of fibrosis and cirrhosis. The demographic and clinical characteristics of patients including age, gender, height, weight, BMI, underlying disease (diabetes, hypertension, ischemic heart disease) and the results of liver function tests including ALT, AST, AlkP, total and direct bilirubin. The results for liver size, fatty liver, and its grade were also recorded. Finally, the results of biopsy and SWE ultrasound of each patient were compared using statistical methods.

Liver ultrasound guided biopsy was performed using a 17-gauge needle. The needle was placed in the middle line of the 9th and 11th Intercostal space and the minimum acceptable sample length was 15 mm. All samples were fixed using formalin and stored in paraffin. Standard histological staining techniques (Hematoxylin and eosin and Trichrome Reticulin) were used to analyze the pathology of the liver samples which, were examined by experienced pathologists who were unaware of the results of the liver imaging.

All patients who underwent liver biopsy during the study were recalled and SWE ultrasound was done by an experienced radiologist to determine the degree of stiffness of the liver. For this purpose, the French supersonic SWE ultrasound was used. The elastography was conducted with the manufacturer's instructions and standard principles. The elastography on the right lobe of the liver was carried out using the M-probe placed on the intercostal space (Trans-Thoracic view) and patients were in the dorsal decubitus position with full abduction of the right arm. By choosing a region of interest (ROI) of 15 mm in each SWE image, the mean and standard deviation of elasticity were shown within the ROI. For each patient, 5 values were calculated and the average of these values was recorded as the result of the liver stiffness in kilopascal units (kPa).

The stages of fibrosis were determined from 0 to 4 according to the METAVIR classification system: [9]

F0 = no fibrosis
F1 = portal fibrosis without septa
F2 = portal fibrosis and few septa
F3 = portal fibrosis with multiple septa and without cirrhosis
F4 = cirrhosis.

STATISTICAL ANALYSIS

SPSS software version 20th was used for statistical analysis. In order to compare the prediction of liver fibrosis grades analysis was performed and the AUC for the different stages of liver fibrosis was calculated. The significance level in the tests was considered to be $P < 0.05$.

RESULTS

In our study, the most of the patients the age group of 41-60 years i.e., 39 out of 70 (55.7%), followed by 21-40 years, i.e., 23 out of 70 (32.8%) in Table 1.

Table-1: Distribution of different age groups of patients

Age in years	No. of patients	Percentage
1-20	7	10.0
21-40	23	32.8
41-60	39	55.7
>61	1	1.4
Total	70	100

Table-2: Distribution of gender

Liver stiffness (kPa)	No. of patients	Percentage
Male	51	72.8
Female	19	27.1
Total	70	100

In table 2, maximum number of patients were male 51 (72.8%) and least were female 19 (27.1%) in our study.

Table-3: distribution of Biochemical Profile

Biochemical Test	Mean± SD
Alanine transaminase (ALT) (IU/L)	87±4.2
Aspartate transaminase (AST) (IU/L)	63±4.5
Alkaline Phosphate (μ/L)	193±12.2
Total Bilirubin (mg/dl)	1.8±0.3
Albumin (g/L)	6.9±1.2

Table-4: Liver stiffness (kPa)

Liver stiffness	Number of patients (%)
F0-F1 (<7.1 kPa)	37 (52.8)
F2 (7.1–9.4 kPa)	13 (18.5)
F3 (9.5–12.4 kPa)	9 (12.8)
F4.1 (12.5–24.9 kPa)	7 (10)
F4.2 (>25 kPa)	4 (5.7)

In table 4, the METAVIR fibrosis grades were as follows: F0-F1 = 37 (52.8%); F2 = 13 (18.5%); F3 = 9 (12.8%); F4.1 = 7 (10%); F4.2 = 4 (5.7%).

Table-4: Hepatic complication of the patients

Hepatic decompensation	Number of patients (%)
Variceal hemorrhage	3 (4.2)
Ascites	3 (4.2)
Hepatic encephalopathy	5 (7.1)
Jaundice	4 (5.7)
Hepatorenal syndrome	1 (1.4)
Spontaneous bacterial peritonitis	1 (1.4)

Table-5: Hepatic complication of the patients

Liver-related events	Number of patients (%)
Hepatocellular carcinoma	1 (1.4)
Liver transplantation	1 (1.4)

In our study 19 patients experienced one or more Liver-related events; the first Liver-related events were: 17 hepatic decompensations (3 variceal bleeding, 3 ascites, 5 Hepatic encephalopathy, 4 Jaundice, 1 Hepatorenal syndrome and 1 Spontaneous bacterial peritonitis), 1 hepatocellular carcinomas. Additionally, throughout the study period, only one patient, who was addicted to drugs, died of septic shock (a cause unrelated to Hepatocellular carcinoma) and this event was not included in the analysis in table 4 and 5.

DISCUSSION

Prognosis and management of chronic liver diseases, including viral hepatitis B and C, are highly dependent on liver fibrosis; therefore evaluating the degree of fibrosis is an important part of managing the patients with chronic liver disease [10]. Although, liver biopsy is the gold standard for liver fibrosis, the invasive nature and rare but high-risk side effects of liver biopsy such as bleeding, pneumothorax, hemothorax, and death, increases the need of non-invasive test to evaluate liver fibrosis [11]. Over the past decade, ultrasound techniques have been widely developed and available to estimate the stage of liver fibrosis. These non-invasive methods are able to evaluate differences in the soft tissue elastic properties by inducing mechanical stress and examining the changes of tissues. The basis of SWE is the production of shear waves by tissue displacement induced by ultrasound beam or external pressure [12]. The aim of this study was to investigate the diagnostic accuracy of SWE as a non-invasive method to predict liver fibrosis by liver stiffness in patients with liver disease with different etiologies, compared to liver biopsy as a gold standard.

In our study, increase in risk of complications that we observed according to liver stiffness categories within the cirrhotic range suggests that TE offers prognostic information above and beyond that provided by liver biopsy. Whereas the stage of cirrhosis is traditionally defined by histological evidence of regenerative nodules with one or two qualitative categories, the dynamic range of LSM is much greater. Since the quantity of fibrous tissue deposition varies widely in cirrhosis, it is clear that the risk of complications is not uniform among cirrhotic patients. In this regard, the ability to express liver stiffness as a continuous variable (from, 12.5 to 75 kPa in cirrhosis) or in an arbitrary number of categories represents an advantage for prognostication compared with biopsy. Indeed, several studies have shown better performance of Scan (and other non-invasive tools) compared with biopsy for predicting hepatic complications [13, 14].

For example, in the study of Vergniol *et al.*, the AUROCs for 5-year survival of FibroScan, FibroTest, and biopsy were 0.82, 0.80, and 0.76, respectively. [15] The AUROC observed for TE (0.80)

in our study is consistent with these reports, and supports its excellent discriminatory ability. At a threshold liver stiffness value <20 kPa, TE had a sensitivity, specificity, and accuracy of 41%, 93%, and 90%, respectively. Liver stiffness values, 20 kPa effectively exclude complications (NPV 97%); however, the PPV of higher results (20%) does not allow one to adequately identify which patients will go on to develop a complication. The latter patients should perhaps undergo enhanced follow-up.

Our study includes several additional findings worthy of discussion. First, we identified an increased risk of complications among patients with liver stiffness corresponding to each of F2, F3, and F4 fibrosis compared with F0–1 fibrosis. For example, patients with liver stiffness between 7.1 and 9.4 kPa (F2) at baseline had a two-fold risk of complications compared with those with lower liver stiffness (F0–1; Table 4). Since progression to cirrhosis over this time frame in a patient with F2 fibrosis is unexpected, we hypothesize that this relates to underestimation of fibrosis by TE in some cases. This is not unexpected since the sensitivity of a liver stiffness >9.5 kPa for advanced fibrosis (F3–F4) is only 73% [16]. Second, our data suggest that the influence of liver stiffness on complications is independent of which Scan probe is used. A unique aspect of our study is the inclusion of patients scanned using the XL probe, not available in most prior studies. Confirmation of this association is important because liver stiffness measured using the XL probe is typically 1–2 kPa lower than with the M probe [17].

Also, we considered the XL probe a surrogate marker for obesity, which we could not reliably identify using our databases. Surprisingly, this was not a significant predictor of complications, although the study may have been underpowered to detect this association. On the contrary, diabetes and coagulopathy were independently associated with complications. Diabetes is an important risk factor for all-cause mortality in general, plus the progression of chronic liver diseases including HBV, HCV, and NAFLD [18]. The association between coagulopathy and liver-related complications is largely due to recorded diagnoses of thrombocytopenia in the administrative data, although some patients had hereditary and acquired coagulation defects. Although we attempted to exclude patients with hepatic decompensation prior to their Scan, it is possible that some patients were coagulopathic, yet clinically compensated. Nevertheless, exclusion of the 123 patients with coagulopathy did not influence the association between liver stiffness and complications (data not shown).

Despite having a small sample size, the present study has considerable strengths. The subjects were living-related liver transplantation donors who were extensively evaluated clinically, chemically, radiologically, and histologically, making this the largest reported cohort of histologically normal livers. The healthy condition of the livers in our subjects was further confirmed intraoperatively during and postdonation. Another important aspect to consider is the large range of LS values obtained in studies that did not rely on histology to define normal liver; studies that include liver histology show a narrower range (< 7.2 kPa) [19-21]. A stiff liver is rarely found in the absence of any pathology. Hence, transient elastography may be used to screen the general population and to identify those that require further evaluation. The LS threshold requires further investigation and should take into account the population demographics as well as the likely prevalence of the condition to be screened for.

CONCLUSION

Liver stiffness measured by TE is an independent predictor of hepatic complications and mortality in patients with chronic liver disease. The risk estimates that we report at clinically relevant liver stiffness cut-offs will provide valuable information to physicians and assist them in counseling their patients regarding their prognosis and may help guide their follow-up.

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