2D Shear Wave Elastography of Liver in Patients with Primary Extrahepatic Portal Vein Obstruction

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Aims: To evaluate liver stiffness (LS) in patients of primary extrahepatic portal vein obstruction (EHPVO) using 2D shear wave elastography (SWE) and compare it with healthy volunteers. **Methods:** Fifty patients (mean age: 22.4 years) of EHPVO and 25 healthy volunteers were included in the study. Liver function tests and viral markers were done in both groups and endoscopy in EHPVO group, followed by ultrasonography and SWE of liver. Liver elastography was done with patients/volunteers in supine position through right intercostal space. The LS for right lobe of liver was recorded in kilopascals. Three such measurements were taken and the mean of both groups were compared. The variables were also correlated with mean LS using Pearson's correlation coefficient in EHPVO group. **Results:** There was no significant difference in the mean LS in patients of EHPVO (5.96 kPa) and healthy volunteers (5.47 kPa) ($P = 0.093$). There was no significant correlation between LS with duration of symptoms, hematemesis, esophageal varices, total bilirubin, serum alkaline phosphatase and aspartate aminotransferase levels in EHPVO group. **Conclusion:** SWE of liver may be used as a simple additional tool in the diagnosis of patients of EHPVO who show LS values similar to normal liver. (J CLIN EXP HEPATOL 2017;7:23–27)

Primary extrahepatic portal vein obstruction (EHPVO) is an idiopathic vasculopathy characterized by occlusion of main and/or right & left branches of portal vein with resultant development of collaterals.¹ There may be associated obstruction of intrahepatic portal vein, splenic vein and superior mesenteric vein. EHPVO leads to pre-hepatic portal hypertension and is the most common cause of gastrointestinal bleeding in children.² Diagnosis is usually by ultrasonography (USG) with color Doppler which shows portal vein replaced by multiple collaterals at porta with or without chronically thrombosed intrahepatic portal, splenic and superior mesenteric veins along with enlarged caudate lobe, prominent hepatic fissures and mild coarsening of parenchymal architecture.³ However, secondary portal vein thrombosis with chronic changes may be seen in up to 25% of patients with cirrhosis of liver and differentiation from EHPVO based on USG and color Doppler may be difficult as vascular and liver morphological changes appear similar.⁴ Laboratory tests and imaging with computed tomography (CT) scan may occasionally help in this differentiation, but

invasive and risky liver biopsy may be needed in difficult cases.^{3,5–8} Liver function is normal and liver fibrosis is rarely seen in EHPVO and hence absence of fibrosis in biopsy specimen favors a diagnosis of EHPVO.^{5,6} There is thus a need for a non-invasive technique which can detect the presence or absence of liver fibrosis and thus differentiate EHPVO from cirrhosis when hepatic morphological changes are similar.

Ultrasound elastography (USE), including 2D shear wave elastography (SWE) is a simple non-invasive technique developed to assess tissue stiffness.^{9–12} The role of USE in patients with EHPVO has not been well evaluated with only one study describing the role of transient elastography in the evaluation of liver and spleen stiffness.¹³ Although, data is available on the role of SWE in assessment of LS in patients of chronic liver disease,^{14,15} there is no data in the literature on its role in patients of EHPVO. Since liver function is usually normal in EHPVO and there is no parenchymal fibrosis, USE, which measures liver fibrosis, must show liver stiffness (LS) similar to healthy adults. Thus we aimed to assess the LS of patients with EHPVO using SWE and compare it with healthy volunteers.

METHODS

This prospective study was performed after obtaining approval from Institute Ethics Committee and informed consent from all patients. All consecutive patients of clinically suspected EHPVO, during the period August 2013 to November 2014, were included in the study. Twenty-five

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healthy volunteers were also included in the study after obtaining informed consent.

A total of 56 patients of suspected EHPVO were initially evaluated clinically followed by laboratory tests and upper gastrointestinal endoscopy (UGIE). Blood investigations included serum bilirubin, alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate transaminase (AST), serum albumin, platelet count and HBsAg and anti-HCV antibodies (markers of hepatitis B and hepatitis C viruses respectively). UGIE was done in all for assessing the presence and grade of esophageal varices, presence of red color sign (RCS), lesser curve extension of the varices, portal hypertensive gastropathy (PHG) and fundal varices. Bleeding varices were treated at the same time. Twenty-five non-diabetic healthy volunteers without any history of past or present illness were evaluated with blood tests only and UGIE was not done. All patients and volunteers with positive hepatitis viral markers and volunteers with fatty liver were excluded from evaluation. Subsequently, USG including SWE was done in both groups within 3 days.

USG was done on Aixplorer ultrasound machine (Supersonic Imagine, Aix-en-Provence, France) with SC6-1 convex transducer, after overnight fast. Gray scale and color Doppler evaluation were done initially followed by elastography. On gray scale USG, liver size and echotexture, biliary radicles, spleen size and ascites were evaluated and on Doppler study, splenic vein, portal vein or cavernoma, superior mesenteric vein, left renal vein and collaterals were assessed. A diagnosis of EHPVO was made based on clinical, laboratory and USG results. SWE of liver was performed through the intercostal space with patient in supine position and right arm abducted. The SWE box was placed on the right lobe of liver about 1.5–2 cm deep to the capsule and in an area free of vessels (Figure 1).¹⁵ With the patients' breath held for 3–5 s, the image was frozen when there was homogeneous color filling. Then a circular region of interest (ROI)—Q box—of size 1 cm diameter was placed on the most homogeneous area within the SWE box to obtain quantitative information of tissue elasticity in kilopascals (kPa) (Figure 1). The measurements were considered reliable when the standard deviation (SD) was less than 10% of the mean LS or when the SD was less than 1 kPa as suggested by the manufacturer. Three such acquisitions were recorded for each patient and average value was noted. Similar evaluation of liver was performed in healthy volunteers. In patients of EHPVO who underwent shunt surgery, liver biopsy was done at surgery and the histopathological results were recorded.

Statistical evaluation of the results was done using SPSS 17 software (SPSS Inc, Chicago, USA). Descriptive statistics was used to summarize characteristics of each study group including mean and standard deviation. Intra-class correlation co-efficient was used to test the reliability of SWE. Comparison of the mean LS in patients of EHPVO and

Figure 1 Ultrasonography image of right lobe of liver with SWE and Q box for measurement of liver stiffness.

healthy volunteers was done using student t test. Correlation of clinical, blood and endoscopic parameters with LS was done using Pearson correlation coefficient. A *P*-value of less than 0.05 was considered significant.

RESULTS

A total of 56 patients of EHPVO were evaluated with SWE. Six patients were excluded (previous shunt surgery – 1; positive HBsAg – 1; non-availability of blood investigation – 1; failed elastography – 3 [unable to hold breath consistently in 2 patients and inability to obtain homogeneous color filling in the SWE box in 1 patient]). Finally fifty patients (mean age: 22.4 years; age range: 13–50 years; 24 males, 26 females) were included in the analysis. The demographic characteristics of the study group is described in Table 1. Twenty five healthy volunteers (mean age: 26.6 years; age range: 18–40 years; 18 males, 7 females) were also included in the study. The liver showed widened fissures and enlarged caudate lobe in all patients. Coarse echotexture was seen in 23 (46%) patients. In 47 patients (94%), both intra and extrahepatic portal vein segments were replaced by collaterals and cavernoma. In remaining 3 patients, two had recanalized portal vein and one had a prominent collateral at porta. The splenic and superior

Table 1 Demographic Parameters and Results of Patients and Healthy Volunteers.

Parameters	EHPVO (n = 50)	Healthy volunteers (n = 25)	P-value
Mean age (years)	22.38 (13–50)	26.56 (18–40)	0.034
Sex (Male:Female)	24:26	18:7	–
Symptoms			
Mean duration (years)	7.22 (1–18)	–	–
Hematemesis (n)	38	–	–
Jaundice (n)	13	–	–
Pain abdomen (n)	22	–	–
Lump (n)	20	–	–
UGI endoscopy			
Esophageal varices – median grade	2 (0–4)	–	–
RCS (n)	14	–	–
PHG (n)	33	–	–
LC extension (n)	15	–	–
Laboratory investigations			
Total bilirubin (mg/dL)	1.93 (0.4–15.5)	0.85 (0.7–1.0)	0.04
Serum Alkaline phosphatase (IU/L)	230.5 (102–624)	112.6 (74–138)	<0.001
Serum AST (IU/L)	44.2 (15–256)	30.7 (21–41)	0.09
Serum ALT (IU/L)	41.2 (14–154)	30.5 (19–38)	0.08
Serum albumin (g/dL)	4.3 (2.5–5.7)	3.9 (3.1–4.7)	0.07
Ultrasonography			
Mean LS (kPa)	5.96 (4.27–8.63)	5.48 (3.53–8.53)	0.093

mesenteric veins were patent in 43 (86%) and 39 (78%) patients respectively. All patients had primary EHPVO without any attributable cause.

The mean LS value in patients of EHPVO was 5.96 (± 1.1) kPa and in healthy volunteers was 5.47

(± 1.3 kPa). There was no significant difference in the mean value between the groups ($P = 0.093$) (Figure 2). The study group included 18 patients with portal biliopathy, who had a mean LS value of 6.47 (± 1.2) kPa. Comparison of LS of EHPVO patients without portal biliopathy ($n = 32$) with that of healthy volunteers ($n = 25$) also showed no significant difference (5.67 kPa and 5.47 kPa respectively; $P = 0.51$). The LS between patients with and without portal biliopathy was significantly different ($P = 0.09$). The reliability of the test (SWE) was assessed by intraclass correlation co-efficient (Cochrane's alpha) of the three LS values measured in each patient which was 0.863 suggesting good correlation.

In patients of EHPVO, there was no significant correlation of LS values with age, hematemesis, grade of esophageal varices, portal hypertensive gastropathy and splenic vein diameter. The LS did not show any significant correlation with duration of symptoms (Pearson's correlation coefficient: 0.26; $P = 0.06$). The LS also did not show any significant correlation with total bilirubin ($P = 0.25$), serum alkaline phosphatase ($P = 0.07$), serum ALT ($P = 0.44$) and serum AST ($P = 0.60$) levels. Hepatic dysfunction was seen in 4 patients, where AST and ALT levels were more than 2 times normal (mean: AST–154.5; ALT–120.3). The mean LS in these 4 patients was 6.68 kPa

Figure 2 Box plot showing the comparison of liver stiffness in the study group (EHPVO) and normal healthy population.

(5.1–7.4 kPa). This was higher than the mean LS of EHPVO group.

Twenty-seven patients were managed with proximal lienorenal shunt surgery and a wedge liver biopsy was obtained in all these patients at surgery. Histopathology showed maintained lobular hepatic architecture and mild periportal inflammation in all the patients. Hepatocyte inflammation was not seen in any of them. Mild periportal fibrosis was seen in only two patients. The mean LS value in these two patients were 8.63 kPa and 5.5 kPa. The former patient had portal biliopathy also. The mean LS value of patients ($n = 25$) without liver fibrosis on biopsy was 5.97 kPa (range: 4.27–7.5 kPa), which was nearly the same as the total mean value (5.96 kPa).

DISCUSSION

Shear wave elastography is a simple and reliable technique for assessment of liver stiffness. Its role in chronic hepatitis and cirrhosis is becoming well established.^{14–17} To the best of our knowledge, this is the first study on evaluation of LS by SWE in patients of EHPVO.

The morphological changes of liver in EHPVO on CT scan has been described in literature.³ Due to ischemia to peripheral portions of liver, there is atrophy of segments 2 & 3 (in about 70% cases) and hypertrophy of segment 4 (in about 50%).³ Caudate lobe enlargement is seen in 85% cases. Right posterior segments may also undergo atrophy. Liver surface nodularity may be rarely seen (less than 10%).³ As these morphological changes are similar to that seen in chronic liver disease, differentiation on routine ultrasonography is often difficult. Performing CT scan routinely in such patients, who are mostly adolescents and young adults, results in exposure to radiation. Histologically, the liver in patients of EHPVO shows maintained lobular architecture with or without ballooning degeneration of hepatocytes and periportal inflammation with lymphocytes and few plasma cells. Interface hepatitis is not seen and fibrosis is uncommon.^{1,13,18} In chronic liver disease, there is deposition of collagen fibers with fibrosis and septations on histology.¹⁹ A chronically diseased liver with morphological changes similar to EHPVO (atrophy-hypertrophy changes) usually shows significant fibrosis which helps in differentiating it from EHPVO.^{20,21} Based on this fact, we found that the published LS values as measured by 2D-SWE in patients of chronic liver disease are usually more than 7.3–7.8 kPa for fibrosis $\geq$ F2.^{22,23} These values are higher than the values of EHPVO group in our study.

In this study the mean LS values of patients of EHPVO and healthy volunteers were similar without any significant difference. The only study in literature assessing liver stiffness by USE in patients of EHPVO was by Sharma et al.,¹³ who found that there was significant difference ($P = 0.001$) in LS values between patients of EHPVO (6.7 kPa) and healthy volunteers (4.6 kPa). However, unlike our study,

they used transient elastography (Fibroscan) in their study. The values for healthy volunteers in their study were lower than that of our study and the values in patients of EHPVO were higher than that of our study. This may be because fibroscan may show fallaciously high LS values in EHPVO due to small right lobe of liver. Further, the LS values in healthy population in the present study were also similar to the values described in literature (4.9–5.5 kPa).^{14,24,25}

Transient elastography (TE; Fibroscan) is the most widely used technique for evaluation of liver stiffness, and is mostly used in the evaluation and follow-up of patients of chronic liver disease and cirrhosis.²⁶ Reference values have been defined in literature to distinguish various stages of fibrosis (F1 to F4; METAVIR scoring) and may replace invasive liver biopsy in such patients. The reproducibility of the results is also high. Studies have compared SWE with TE and showed good correlation between each other and with liver biopsy.^{17,22} Recent guidelines by European Federation of Societies for Ultrasound in Medicine and Biology suggest measurement at 3–7 cm depth for SWE.²⁷ Since in SWE, a 2D gray scale image is available on which LS can be measured, theoretically it should be better than TE in avoiding artifacts due to vessels and adjacent tissues, especially in patients of EHPVO who have smaller liver.¹⁵ Studies comparing these two techniques in EHPVO are however needed to confirm this. It is however known that SWE is better than TE in patients with ascites.^{26,28} Reproducibility of SWE is good in expert hands. For valid result of fibroscan, 10 measurements are taken and median value is used. However, for 2D-SWE, studies have suggested that 3 measurements are sufficient and mean value is to be used for calculation.^{29,30} We also followed the same in the present study. However, a recent consensus has suggested 10 acquisitions and use of the median.²⁶ This would increase the duration of scan. The location of placement of ROI is also important with most studies suggesting it should be placed 2 cm deep to the capsule but not more than 5 cm deep, avoiding major vessels and rib shadows.^{24,26,31,32} We also followed similar protocol.

The mean LS did not show any correlation with esophageal varices, LC extension, RCS and PHG. This could be explained by the fact that in EHPVO, it is the prehepatic obstruction which causes portal hypertension.² The morphological changes in liver occur secondary to portal vein obstruction and are not the cause for it. Possibly for the same reason, mean LS did not show any correlation with splenic vein diameter or spleen size.

There were some limitations in our study. First, histopathology was not available in all patients. Hence, accurate assessment of extent of fibrosis in patients of EHPVO could not be assessed. Secondly, we did not compare the values with patients of chronic liver disease or cirrhosis. This would have helped in better distinguishing the two diseases. Thirdly some patients had portal biliopathy which may have affected the true stiffness values of liver.^{33,34}

In conclusion, SWE is a simple technique which can be used as an adjunct to sonography in the evaluation of liver in patients of EHPVO. The normal liver stiffness in patients of EHPVO may help in distinguishing this entity from cirrhosis on ultrasonography especially when the morphological features are misleading. Its routine use may obviate an invasive liver biopsy in difficult cases.

CONFLICTS OF INTEREST

The authors have none to declare.

REFERENCES

1. Sarin SK, Sollano JD, Chawla YK, et al. Consensus on extra-hepatic portal vein obstruction. *Liver Int.* 2006;26:512–519.
2. Gauthier F. Recent concepts regarding extra-hepatic portal hypertension. *Semin Pediatr Surg.* 2005;14:216–225.
3. Vilgrain V, Condat B, Bureau C, et al. Atrophy-hypertrophy complex in patients with cavernous transformation of the portal vein: CT evaluation. *Radiology.* 2006;241:149–155.
4. Francoz C, Belghiti J, Vilgrain V, et al. Splanchnic vein thrombosis in candidates for liver transplantation: usefulness of screening and anticoagulation. *Gut.* 2005;54:691–697.
5. Rangari M, Gupta R, Jain M, Malhotra V, Sarin SK. Hepatic dysfunction in patients with extra-hepatic portal venous obstruction. *Liver Int.* 2003;23:434–439.
6. Peter L, Dadhich SK, Yachha SK. Clinical and laboratory differentiation of cirrhosis and extrahepatic portal venous obstruction in children. *J Gastroenterol Hepatol.* 2003;18:185–189.
7. Malik R, Lai M, Sadiq A, et al. Comparison of transient elastography, serum markers and clinical signs for the diagnosis of compensated cirrhosis. *J Gastroenterol Hepatol.* 2010;25:1562–1568.
8. Friedman LS. Controversies in liver biopsy: who, where, when, how, why? *Curr Gastroenterol Rep.* 2004;6:30–36.
9. Sporea I. Is there a real future for liver elastography? *J Gastrointest Liver Dis.* 2012;21:129–131.
10. Talwalkar JA, Kurtz DM, Schoenleber SJ, West CP, Montori VM. Ultrasound-based transient elastography for the detection of hepatic fibrosis: systematic review and meta-analysis. *Clin Gastroenterol Hepatol.* 2007;5:1214–1220.
11. Koizumi Y, Hirooka M, Kisaka Y, et al. Liver fibrosis in patients with chronic hepatitis C: noninvasive diagnosis by means of real time tissue elastography-establishment of the method for measurement. *Radiology.* 2011;258:610–617.
12. Friedrich-Rust M, Nierhoff J, Lupsor M, et al. Performance of acoustic radiation force impulse-imaging for the staging of liver fibrosis: a pooled meta-analysis. *J Viral Hepat.* 2012;19:e212–e219.
13. Sharma P, Mishra SR, Kumar M, Sharma BC, Sarin SK. Liver and spleen stiffness in patients with extrahepatic portal vein obstruction. *Radiology.* 2012;263:893–899.
14. Ferraioli G, Tinelli C, Zicchetti M, et al. Reproducibility of real-time shear wave elastography in the evaluation of liver elasticity. *Eur J Radiol.* 2012;81:3102–3106.
15. Ferraioli G, Tinelli C, Bello BD, Zicchetti M, Filice G, Filice C. Accuracy of real-time shear wave elastography for assessing liver fibrosis in chronic hepatitis C: a pilot study. *Hepatology.* 2012;56:2125–2133.
16. Grgurevic I, Puljiz Z, Brnic D, et al. Liver and spleen stiffness and their ratio assessed by real-time two dimensional-shear wave elastography in patients with liver fibrosis and cirrhosis due to chronic viral hepatitis. *Eur Radiol.* 2015;25:3214–3221.
17. Gerber L, Kasper D, Fitting D, et al. Assessment of liver fibrosis with 2-D shear wave elastography in comparison to transient elastography and acoustic radiation force impulse imaging in patients with chronic liver disease. *Ultrasound Med Biol.* 2015;41:2350–2359.
18. Weiss B, Shteyer E, Vivante A, et al. Etiology and long-term outcome of extrahepatic portal vein obstruction in children. *World J Gastroenterol.* 2010;16:4968–4972.
19. Standish RA, Cholongitas E, Dhillon A, Burroughs AK, Dhillon AP. An appraisal of the histopathological assessment of liver fibrosis. *Gut.* 2006;55:569–578.
20. Moon KM, Kim G, Baik SK, et al. Ultrasonographic scoring system score versus liver stiffness measurement in prediction of cirrhosis. *Clin Mol Hepatol.* 2013;19:389–398.
21. Colli A, Fraquelli M, Andreoletti M, Marino B, Zuccoli E, Conte D. Severe liver fibrosis or cirrhosis: accuracy of US for detection – analysis of 300 cases. *Radiology.* 2003;227:89–94.
22. Sporea I, Bota S, Gradinaru-Tascau O, Sirli R, Popescu A, Jurchiş A. Which are the cut-off values of 2D-Shear Wave Elastography (2D-SWE) liver stiffness measurements predicting different stages of liver fibrosis, considering Transient Elastography (TE) as the reference method? *Eur J Radiol.* 2014;83:e118–e122.
23. Samir AE, Dhyani M, Vij A, et al. Shear-wave elastography for the estimation of liver fibrosis in chronic liver disease: determining accuracy and ideal site for measurement. *Radiology.* 2015;274:888–896.
24. Huang Z, Zheng J, Zeng J, Wang X, Wu T, Zheng R. Normal liver stiffness in healthy adults assessed by real-time shear wave elastography and factors that influence this method. *Ultrasound Med Biol.* 2014;40:2549–2555.
25. Hudson JM, Milot L, Parry C, Williams R, Burns PN. Inter- and intra-operator reliability and repeatability of shear wave elastography in the liver: a study in healthy volunteers. *Ultrasound Med Biol.* 2013;39:950–955.
26. Barr RG, Ferraioli G, Palmeri ML, et al. Elastography assessment of liver fibrosis: society of radiologists in ultrasound consensus conference statement. *Radiology.* 2015;276:845–861.
27. Cosgrove D, Piscaglia F, Bamber J, et al. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 2: Clinical applications. *Ultraschall Med.* 2013;34:238–253.
28. Poynard T, Munteanu M, Luckina E, et al. Liver fibrosis evaluation using real-time shear wave elastography: applicability and diagnostic performance using methods without a gold standard. *J Hepatol.* 2013;58:928–935.
29. Sporea I, Gradinaru-Tascau O, Bota S, et al. How many measurements are needed for liver stiffness assessment by 2D-shear wave elastography (2D-SWE) and which value should be used: the mean or median? *Med Ultrason.* 2013;15:268–272.
30. Leung VY, Shen J, Wong VW, et al. Quantitative elastography of liver fibrosis and spleen stiffness in chronic Hepatitis B carriers: comparison of shear-wave elastography and transient elastography with liver biopsy correlation. *Radiology.* 2013;269:910–918.
31. Procopet B, Berzigotti A, Abraldes JG, et al. Real-time shear-wave elastography: applicability, reliability and accuracy for clinically significant portal hypertension. *J Hepatol.* 2015;62:1068–1075.
32. Wang CZ, Zheng J, Huang ZP, et al. Influence of measurement depth on the stiffness assessment of healthy liver with real-time shear wave elastography. *Ultrasound Med Biol.* 2014;40:461–469.
33. Kalra N, Shankar S, Khandelwal N. Imaging of portal cavernoma cholangiopathy. *J Clin Exp Hepatol.* 2014;4(Suppl 1):S44–S52.
34. Dhiman RK, Saraswat VA, Valla DC, et al. Portal cavernoma cholangiopathy: consensus statement of a working party of the Indian national association for study of the liver. *J Clin Exp Hepatol.* 2014;4(Suppl 1):S2–S14.