ORIGINAL ARTICLE

Comparison between Doppler Ultrasound Findings in Liver Blood Flow and Supersonic Shearwave Imaging for Non-invasive Assessment of Liver Fibrosis

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ABSTRACT

Background: Liver biopsy is gold standard but invasive for assessing liver fibrosis, non-invasive tests have gained increasing importance.
Aim: To compare the Doppler ultrasound findings in the liver blood flow and elastography for noninvasive evaluation of liver fibrosis.
Methods: The present investigation was an analytical epidemiologic study in which 122 patients (59 males and 63 females) with chronic liver disease were divided into two groups (Forty-five cases with clinically significant fibrosis (≥F2) and 77 cases with clinically insignificant fibrosis). Doppler ultrasound and Supersonic Shearwave Imaging (SSI) were used for assessment purposes. Mann-Whitney and Pearson Tests as well as shear point values were used to analyze the collected data.
Results: The mean and standard deviation of the patients' age were 51±4.31 years. In anticipating liver fibrosis stage ≥FII, Hepatic vein resistance index (HVRI) showed a high consistency (AUROC of 0.89 ± 0.011 for FII or more, the HVRI<0.95 with a 90% specificity and 97% sensitivity) compared to pathology and was approximate to SSI analysis. SSI and HVRI show significant changes in clinically significant fibrosis (≥F2) versus no or minimal fibrosis (p<0.001).
Conclusion: Resistance index of hepatic vein flow is a helpful means in noninvasive assessment of hepatic fibrosis stage FII or higher and might assist reducing the number of biopsies required.
Keyword: SSI, Ultrasound Doppler, Liver fibrosis

INTRODUCTION

Liver diseases are some of the most common diseases. Research findings suggest that liver disease has affected more than 500 million people in the world.[1] Advanced stages of liver disease often result in fibrosis, indicating the excessive accumulation of extracellular matrix protein[1,2]. Liver fibrosis is caused by several factors some of which include viral infections, excessive alcohol consumption, and non-alcoholic steatohepatitis[2,3]. Non-alcoholic fatty liver is generally recognized as one of the main causes of chronic liver disease[4]. The best method for diagnosing non-alcoholic liver disease is liver biopsy and histological study, which provides several categories based on histological pathological research[5,6,7,8], however liver biopsy sampling has some limitations such as the invasive nature of the sampling, high cost, side effects, the low level of individual satisfaction, and sampling differences[1,4,5]. Therefore, some sources have reported that the mortality rate following the liver biopsy sampling was 1 case per 10,000 people[4]. Meanwhile, it should be pointed out that patients with liver fibrosis, in advanced conditions, suffer from ascites and coagulation disorders which are side effects of liver biopsy sampling. On the other hand, liver biopsy cannot be used to follow up the disease.[7] Therefore, less invasive methods have recently been considered by physicians[8]. One of these methods is known as Doppler ultrasound. It is a non-invasive method for studying hemodynamic of liver vessels in patients with liver disease.[1] Variations in liver blood flow can indicate the severity of liver parenchymal diseases as well as their complications, including port hypertension, cirrhosis, and steatosis. The standard blood flow rate in liver veins, portal vein and liver arteries has been measured in studies such as Coulden et al[9]. Liver blood circulation is dependent on severity of fibrosis because the flexibility of the arterial walls in the liver reflects variations in the liver parenchyma which results from the scars in the liver tissue. Bolondi et al. showed that the Doppler signal from the right hepatic vein varies from a triphasic flow to a monophasic flow during cirrhosis[10]. In several studies, variations in constant Doppler parameters and histological findings, such as inflammation and steatohepatitis, have been measured using imaging and blood tests. Despite all these advances, there is still no consistent, accurate, non-invasive method to diagnose liver fibrosis[4]. Recently, researchers have presented a non-invasive and new method for diagnosing liver fibrosis. In this method, an instrument called elastometer with accuracy of about 85% is used to calculate liver fibrosis[4,5]. Generally, in this method, the M probe examines the right lobe of the liver for viscosity of the tissue through transthoracic view. Supersonic Shear Imagine (SSI) has been developed to determine liver stiffness through the quantification of mechanical or ultrasound shear wave propagation through the hepatic parenchyma. Many researches have confirmed the capability and reproducibility of this method in the detection of severe liver fibrosis in patients with chronic viral hepatitis[11].

This study aimed to compare the Doppler ultrasound in the liver blood flow and SSI for non-invasive evaluation of liver fibrosis.

MATERIALS AND METHODS

In this study, 122 patients (59 males and 63 females) with pathologically proved chronic liver disease undergo Doppler ultrasound and SSI.

Patients who had undergone a liver biopsy within a month, referred for Doppler ultrasound and SSI. The pathologic stage of fibrosis was used to compare SSI and hepatic vessels Doppler findings.

Doppler ultrasound: The Doppler ultrasound (An AixPlorer scanner, Supersonic, Paris, France, incorporating a curvilinear transducer, 1–6 MHz) parameters in the present study included hepatic vein resistance index (HVRI), hepatic artery resistance index (HARI), and portal vein maximum flow. In order to avoid bias, Doppler diagnostic procedures were carried out by two different radiologists, each of whom had at least 2 years of practice on hepatic Doppler analysis. The HVRI was defined as the lowest negative velocity minus the highest negative velocity (or positive velocity in patients with low triphasic waveforms) divided by the highest negative velocity.

Prior to Doppler ultrasound, all patients were kept fasting for at least 6 hours[8].

Supersonic Shear wave Imaging (SSI): The shear wave elastography was performed (An AixPlorer scanner, Supersonic, Paris, France, curvilinear transducer, 1–6 MHz) by an experienced radiologist based on the factory's description through the transthoracic view on the right hepatic lobe. Ten correct measurements and an interquartile range (IQR) below 20% were considered for the assessment.

Statistical Analysis of Data: In order to compare the quantitative variables of the two groups, U-Mann Whitney Test was used. In addition, Pearson correlation coefficient was used to investigate the relationship between the variables. All statistical analyses were performed at the significance level of $p < 0.05$, using SPSS 23.

RESULTS

Descriptive statistics for demographic characteristics of the units under study: Out of 122 patients in the study, 59 were males and 63 were women. Fisher's Exact Test showed that there was no significant difference between the two groups in terms of age and sex. Therefore, the two groups had a good homogeneity for data analysis (Table1).

The results of the Mann-Whitney Test (Table 2) show that there was a significant difference between the two groups in terms of HVRI, The higher fibrosis (≥FII), the lower the hepatic vein resistance index.

The results of the Mann-Whitney Test (Table 3) show that there was no significant difference between the two groups in terms of HARI. By an increase in fibrosis (≥FII), the hepatic artery resistance index did not change significantly.

The results of the Kolmogorov-Smirnov Test (Table 4) showed that the distribution of the portal vein maximum flow in the two groups was not normal ($p = 0.001$). Therefore, the nonparametric Mann-Whitney Test was used to compare the two groups for portal vein maximum flow.

The results of the Mann-Whitney Test (Table 4) show that there was a significant difference between the two groups in terms of portal vein maximum flow. Furthermore, with a significant increase in fibrosis (≥FII), the portal vein maximum flow was significantly changed. Accordingly, it decreased from 20 cm/s to 18.88 cm/s.

The result of the Mann-Whitney Test (Table 5) showed that there was a significant difference between the two groups in terms of SSI. Furthermore, with an increase in fibrosis (≥FII), the values of SSI were significantly changed. Accordingly, the values increased from 6.99 kPa to 12.09 kPa.

The results demonstrate that the area under the curve (AUROC) analysis of SSI in comparison to fibrosis scored by liver biopsy revealed an AUROC of 0.878 ± 0.049 for diagnosis of fibrosis staged FII or more with 85 % sensitivity and 89 % specificity at a SSI level of 8.35 kPa (Table 6).

In anticipating liver fibrosis stage ≥FII, HVRI showed a high consistency (AUROC of 0.89 ± 0.011 for FII or more, the HVRI<0.95 with a 90% specificity and 97% sensitivity) compared to pathology and was approximate to SSI analysis. SSI and HVRI show significant changes in clinically significant fibrosis (≥F2) versus no or minimal fibrosis ($p<0.001$).

The results of Table 7 showed that the results of SSI can be a good predictor of high fibrosis. It was also found that there was a positive and significant relationship between SSI and liver fibrosis.

Table 1 Characteristics of patients

Fibrosis stage	F0	F1	F2	F3	F4
Age (mean years ± SD)	51.2±7	50±5.1	49.3±6.5	53.1±9	52.7±8.8
Sex (M/F)	20/19	17/21	9/9	7/6	6/8
HVRI (mean ± SD)	1.35 ± 0.05	1.24 ± 0.09	0.80 ± 0.08	0.73 ± 0.12	0.61± 0.12
HARI (mean ± SD)	0.66 ± 0.65	0.66 ± 0.15	0.69 ± 0.05	0.71 ± 0.02	0.65 ± 0.01
Portal vein maximum flow (mean cm/s ± SD)	21 ± 4.9	20.3 ± 2.8	19 .9 ± 9.7	18.1 ± 2.6	18 ± 1.9
SSI (mean kPa ± IQR)	6.5±1.2	7±2.3	8.4±4.9	12±5.7	17±4.5

SD standard deviation, HVRI hepatic vein resistance index, HARI hepatic artery resistance index, IQR interquartile range, SSI supersonic shear imaging

Table 2: HVRI difference between two groups

HVRI/Groups	Mean ± Standard Deviation	Kolmogorov-Smirnov	P (Mann Whitney)
F0-FI	1.33±0.11	0.001	0.OO1
≥FII	0.78±0.26		

Table 3. HARI difference between two groups

Portal vein maximum flow/Groups	Mean ± Standard Deviation	Kolmogorov-Smirnov	P (Mann Whitney)
F0-FI	0.66±0.035	0.001	0.61
≥FII	0.67±0.034		

Table 4. Portal vein maximum flow differences between two groups

Portal vein maximum flow/Groups	Mean ± Standard Deviation	Kolmogorov-Smirnov	P (Mann Whitney)
F0-FI	20.64±1.27	0.001	0.001
≥FII	18.88±1.63		

Table 5: SSI value difference between two groups

Groups/SSI	Mean ± IQR	Kolmogorov-Smirnov	P (Mann Whitney)
F0-FI	6.99±1.23	0.001	6.99±1.23
≥FII	12.09±3.41		

Table 6. The cut-off point values of Doppler parameters for high fibrosis

Doppler parameters	Cut-off	Sensitivity%	Specificity%	AUROC
HVRI	0.95	97	90	0.89
HARI	0.65	51.7	49.9	0.52
Portal vein maximum flow	19.93	19.2	30.1	0.19

Table 7: The cut-off point values of elastography parameters for high fibrosis

	Cut-off	Sensitivity%	Specificity%	AUROC
SSI	8.35	85	89	0.87

DISCUSSION

The results showed that is a normal situation in which an increase in the age is associated with high fibrosis[5]. Studied 102 people with chronic liver disease. The younger subjects were assigned to F0-FI, and older subjects were significantly classified in the ≥ FII. In the present study, it was also found that the group F0-FI had an average age of 50.24 years, while the group ≥FII had an average age of 52.31 years.

The results of the Mann-Whitney Test showed that the hepatic vein resistance index was significantly different in the two groups of F0-FI and ≥FII. In the group with low fibrosis, this index was 1.33 and in the other group 0.78. Moreover, Pearson Correlation Test showed that there was a significant negative relationship between HVRI and liver fibrosis. This means that with an increase in fibrosis, this index reduced.

In the present study for a HVRI value<0.95, sensitivity and specificity were 97 and 90 % for detection of fibrosis staged FII or higher. There was no significant relationship between hepatic artery resistance index and liver fibrosis. Moreover, Mann-Whitney Test showed that the mean hepatic artery resistance index was not significantly different in the two groups (F0-FI, 0.66) (≥FII, 0.67). However, it does not seem to be consistent with most other research studies obtained a similar result[5,12,13,14]. The sensitivity and specificity were 51.7 and 49.9, respectively. In addition, the coverage under the curve was 0.52.

The results of the Mann-Whitney Test showed that with an increase in liver fibrosis (group ≥FII), the portal vein maximum flow reached from 20.64cm/s to 18.88cm/s, which is a significant difference. Additionally, the results of Pearson Correlation Test showed that there was a significant negative relationship between the portal vein maximum flow and liver fibrosis. The results of this study are not consistent with the research by Alempijevic et al who observed that portal vein maximum flow could not predict liver fibrosis[5]. Moreover, the sensitivity and specificity of the portal vein maximum flow were 19.2 and 30.1, respectively.

The results of the Mann-Whitney Test on the values of SSI for the assessment of liver fibrosis showed that there was a significant difference between the mean value (6.99kPa) for the group F0-FI and the mean value (12.09±3.41kPa) for the group ≥FII. The correlation between SSI and liver fibrosis was also found to be positive and significant. It was shown that SSI is by far the most common non-invasive non-clinical tool for diagnosing liver fibrosis[5].

SSI revealed an AUROC of 0.878±0.049 for diagnosis of fibrosis staged FII or more with 85 % sensitivity and 89% specificity at a SSI level of 8.35 kPa. Other studies have also reported a high degree of accuracy for diagnosing liver fibrosis by elastography[15,16].

CONCLUSION

Liver biopsy is a valuable standard for assessing liver fibrosis; however, due its potential for adverse effects and prohibition of global use, non-invasive tests have gained increasing importance. Many non-invasive methods are noteworthy to predict the presence of clinical liver fibrosis; however, no single method has been identified that is superior to other methods. In the present study, it was found that elastography can be of great value for diagnosing fibrosis. It seems that there is an urgent need for reliable non-invasive fibrosis markers to predict the progression of disease in patients with chronic liver disease. However, elastography is still not feasible for predicting all different causes of liver disease, and it is not available in all centers. In the future, it seems that non-invasive methods will be increasingly used to diagnose liver fibrosis. HVRI is a helpful means in noninvasive

assessment of hepatic fibrosis stage FII or higher and assist decreasing the number of biopsies required.

REFERENCES

1. Bernatik T, Strobel D, Hahn EG, Becker D. Doppler measurements: a surrogate marker of liver fibrosis? *European journal of gastroenterology & hepatology* Apr 2002;14(4):383-387.
2. Zhao J, Zhai F, Cheng J, He Q, Luo J, Yang X, Shao J, Xing H. Evaluating the Significance of Viscoelasticity in Diagnosing Early-Stage Liver Fibrosis with Transient Elastography. *PloS one* 2017;12(1):e0170073.
3. van Katwyk S, Coyle D, Cooper C, et al. Transient elastography for the diagnosis of liver fibrosis: a systematic review of economic evaluations. *Liver international : official journal of the International Association for the Study of the Liver* Jun 2017;37(6):851-861.
4. Hashemi SA, Alavian SM, Gholami-Fesharaki M. Assessment of transient elastography (FibroScan) for diagnosis of fibrosis in non-alcoholic fatty liver disease: A systematic review and meta-analysis. *Caspian journal of internal medicine* Fall 2016;7(4):242-252.
5. Alempijevic T, Zec S, Nikolic V, Veljkovic A, Stojanovic Z, Matovic V, Milosavljevic T. Doppler ultrasonography combined with transient elastography improves the non-invasive assessment of fibrosis in patients with chronic liver diseases. *Medical ultrasonography* Jan 31 2017;19(1):7-15.
6. Aube C, Winkfield B, Oberti F, Vuillemin E, Rousselet MC, Caron C, Cales P. New Doppler ultrasound signs improve the non-invasive diagnosis of cirrhosis or severe liver fibrosis. *European journal of gastroenterology & hepatology* Aug 2004;16(8):743-751.
7. Lutz HH, Gassler N, Tischendorf FW, Trautwein C, Tischendorf JJ. Doppler ultrasound of hepatic blood flow for noninvasive evaluation of liver fibrosis compared with liver biopsy and transient elastography. *Digestive diseases and sciences* Aug 2012;57(8):2222-2230.
8. Lutz HH, Schroeter B, Kroy DC, Neumann U, Trautwein C, Tischendorf JJ. Doppler Ultrasound and Transient Elastography in Liver Transplant Patients for Noninvasive Evaluation of Liver Fibrosis in Comparison with Histology: A Prospective Observational Study. *Digestive diseases and sciences* Sep 2015;60(9):2825-2831.
9. Coulden RA, Lomas DJ, Farman P, Britton PD. Doppler ultrasound of the hepatic veins: normal appearances. *Clinical radiology* Apr 1992;45(4):223-227.
10. Bolondi L, Li Bassi S, Gaiani S, Zironi G, Benzi G, Santi V, Barbara L. Liver cirrhosis: changes of Doppler waveform of hepatic veins. *Radiology* Feb 1991;178(2):513-516.
11. Cassinotto C, Boursier J, de Ledinghen V, et al. Liver stiffness in nonalcoholic fatty liver disease: A comparison of supersonic shear imaging, FibroScan, and ARFI with liver biopsy. *Hepatology (Baltimore, Md)* Jun 2016;63(6):1817-1827.
12. Piscaglia F, Gaiani S, Calderoni D, Donati G, Celli N, Gramantieri L, Crespi C, Bolondi L. Influence of liver fibrosis on hepatic artery Doppler resistance index in chronic hepatitis of viral origin. *Scandinavian journal of gastroenterology* Jun 2001;36(6):647-652.
13. Glisic TM, Perisic MD, Dimitrijevic S, Jurisic V. Doppler assessment of splanchnic arterial flow in patients with liver cirrhosis: correlation with ammonia plasma levels and MELD score. *Journal of clinical ultrasound : JCU* Jun 2014;42(5):264-269.
14. Abhilash H, Mukunda M, Sunil P, Devadas K, Vinayakumar KR. Hepatic artery duplex Doppler ultrasound in severe alcoholic hepatitis and correlation with Maddrey's discriminant function. *Annals of gastroenterology* Apr-Jun 2015;28(2):271-275.
15. Kim SU, Kim BK, Han KH. Clinical application of liver stiffness measurement using transient elastography: a surgical perspective. *Digestion* 2013;88(4):258-265.
16. Dincses E, Yilmaz Y. Diagnostic usefulness of Fibro Meter VCTE for hepatic fibrosis in patients with nonalcoholic fatty liver disease. *European journal of gastroenterology & hepatology* Oct 2015;27(10):1149-1153