Diagnostic Accuracy of Hepatic Vein Resistive Index in Detection of Hepatic Fibrosis in Patients of Chronic Liver Disease

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Author's Contribution

[1,2,3,4] *Conception of study*
[1,2,3,5] *Experimentation/Study conduction*
[1,2,3,4,5] *Analysis/Interpretation/Discussion*
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Abstract

Introduction: If we could prove the diagnostic accuracy of hepatic vein resistive index in detecting liver fibrosis in chronic liver disease patients, this would be beneficial for the patients as it is a non-invasive, readily available, and cost-effective technique for the diagnosis of liver fibrosis. This will help the physicians in the early initiation of definitive management.

Materials and Methods: Seventy-five (n=75) patients with hepatitis B aged between 18-50 years were enrolled. Hepatic vein resistive index and liver biopsy were performed in even-patients. Sensitivity, Specificity, PPV, NPV, and overall accuracy of the hepatic vein resistive index was calculated.

Results: Average age group studied was 38y ± 8.2 SD. 57.3 % (N=43) were males and 42.7% (n=32) patients were females respectively. Data of this work Exhibits various statistical indicators 77%. 96.7%. 97.2%. 74.3% and 85.3% respectively.

Conclusion: Hepatic vein resistive index measured by ultrasonography can detect liver fibrosis in CLD with overall sensitivity, Specificity, PPV, NPV, and accuracy of 77.7%. 96.7%. 97.2%. 74.3% and 85.3% respectively.

Keywords: Diagnostic accuracy, chronic liver disease, hepatic vein resistive index, hepatic fibrosis.

Introduction

Chronic liver disease is a progressive condition that leads eventually to liver fibrosis and liver failure.[1-2] Hepatobiliary disorders are commonly seen in clinical practice nowadays among which patients with hepatitis B and C are most commonly encountered.[3-4] Hepatic fibrosis is characterized by the formation of hepatic scars which leads to cirrhosis.[5] Chronic liver disease has many causative etiologies including viral infections, alcohol overdose, steatotic liver disease, primary sclerosing cholangitis, autoimmune disease, and hemochromatosis.[6-8] The incidence of hepatitis B infection depends upon geographical location and is increasing annually ranging between 3% and 9%.[9] The predictors of rising mortality in hepatitis B virus-associated mortality patterns are age over 45 years at the time of diagnosis, male sex, and history of alcoholism and nosocomial risk factors.[10-11] The overall burden of Hepatitis B Virus infection is being recognized increasingly.[12-13] As liver cirrhosis progresses, there is an alteration in the liver parenchyma, and this fibrosis also affects the walls of hepatic veins which increases resistance in the hepatic veins thus leading to an increase in the resistive index on color Doppler examination which helps detect stage fibrosis/cirrhosis.[14-17] Hepatic venous Doppler is a readily available, cheap, simple, and non-invasive procedure.

Local studies are deficient in cirrhosis determined by HVRI compared with liver biopsy.[18] Depending upon the results of this study, the Hepatic vein resistive index by Doppler ultrasound can reliably be applied to avoid undue liver biopsies.

Materials and Methods

Study Objective: To determine the diagnostic accuracy of hepatic vein resistive index in the detection of hepatic fibrosis in patients of chronic liver disease keeping liver biopsy (histopathology) as the gold standard.

Study Design: Cross-sectional validation study.

Settings: The study was done in the Radiology Department, RMC, and Allied Hospitals, Rawalpindi, in association with the Pathology department.

Duration: Six months (22-09-2015 to 21-03-2016).

Sample Size: The study included 75 patients.

Sampling Technique: Non-probability Consecutive sampling technique.

Sample Selection:

a) Inclusion Criteria:

1) Positive PCR of the hepatitis B virus.
    PCR measured by quantitative method;
    - Patients with e antigen-positive having a viral load of 20,000 IU/ml.
    - Patients with e antigen-negative having a viral load of 2000 IU/ml.
2) Age between 18 years and 50 years (both gender).

b) Exclusion Criteria:

1) Patients having splenomegaly.
2) Patients who are on interferon therapy.
3) Patients having esophageal varices.

Data collection procedure: After approval by the ethical committee of Rawalpindi medical college and Allied hospitals, patients fulfilling the inclusion criteria were subjected to Doppler ultrasound of hepatic vein. Informed consent was obtained from all the patients and the procedure was explained to all patients. The procedure was carried out with a pulsed Doppler flowmeter by using a 5MHz convex curvilinear transducer.

Hepatic vein resistive index is calculated by using the formula "maximum negative velocity minus minimum negative velocity (or positive velocity in case of a triphasic flow signal)/maximum negative velocity".

HVRI=$\frac{\text{maximum negative velocity-minimum negative velocity}}{\text{Maximum negative velocity}}$

F0=1.45 ± 0.02
F1=1.26 ± 0.05
F2=1.06 ± 0.06
F3=0.87 ± 0.08
F4=0.46 ± 0.12

In my study fibrosis stage, F2 ≥ will be considered positive for fibrosis.

The results were then compared with a liver biopsy performed by the medicine department MU1 and histological staging analyzed by the pathology department of the same hospital. A liver biopsy specimen was obtained by a pathologist and blindly reviewed. The METAVIR staging system of the degree of fibrosis and cirrhosis was used in liver biopsy specimen interpretation by the pathology department. Fibrosis is staged from 0 to 4 according to METAVIR SYSTEM.

    F0=No fibrosis
    F1=portal fibrosis without septa
    F2=portal fibrosis with few septa
    F3=portal fibrosis with numerous septa without cirrhosis
    F4=cirrhosis

In my study fibrosis is considered from stage FI to F4.
Data Analysis: Data was entered on computer software SPSS version 11.

Results

A total of seventy-five (n=75) patients age between 18-50 years having clinical besides laboratory evidence of chronic liver disease and positive PCR of hepatitis B were enrolled. Subjects with a history of splenomegaly, interferon therapy, and having esophageal varices were excluded from the study. Informed consent was taken from each patient. Doppler ultrasound of the hepatic vein was performed of every patient and HVRI was measured.
Results of the Doppler ultrasound were compared with liver biopsy findings. 57.3% (n=43) males having a mean age of 38.6 years ± 8.2 SD and 42.7% (n=32) were females having a mean age of 37.1 years ± 8.7 SD. There were 54.7% (n=41) of patients who were between age 18-40 years and 45.3% (n=34) were greater than 40 years of age. Demographic results are shown in Tables 1 and 2.

Table 1: Gender and age distribution of subjects

Gender	Number (%)	Mean Age ± SD (years)
Male	43 (57.3%)	38.6 ± 8.2
Females	32 (42.7%)	37.1 ± 8.7
Total	75 (100%)	38.0 ± 8.4

Table 2: Different age groups in the study population

Age Groups (yrs)	Frequency	Percent	Cumulative Percent
18-40	41	54.7	54.7
>40	34	45.3	100
Total	75	100.0	

Results of ultrasound showed 48.0% (n=36) positive and 52.0% (n=39) negative as per our operational definition (Table 3). Liver biopsy results showed that 60% (n=45) of patients were positive and 40% (n=30) were negatives as per criteria defined in our operational definition (Table 4). Cross-tabulation of ultrasound (HVRI) and liver biopsy results are shown in (Table 5).

Table 3: Ultrasound (HVRI) results

	Frequency	Percent	Cumulative Percent
Positive	36	48	48
Negative	39	52	100
Total	75	100	

Table 4: Liver biopsy

	Frequency	Percent	Cumulative Percent
Positive	45	60	60
Negative	30	40	100
Total	75	100.0	

Table 5: Cross-tabulation of ultrasound (HVRI) and liver biopsy results

	LIVER BIOPSY FINDINGS		
Ultrasound	Positive	NEGATIVE	Total
Positive	35 (True Positives)	1 (False Positives)	36
Negative	10 (False Negatives)	29 (True Negatives)	39
Total	45	30	75

Discussion

Liver biopsy remains the typical procedure to diagnose the level of fibrosis in chronic liver disease but it is an invasive procedure and may lead to serious complications if not performed properly.[19] The hepatic venous resistive index has been investigated using color Doppler ultrasonography as a non-invasive technique in CLD, especially in subjects having portal hypertension, portal vein thrombosis, and also in Budd-chiari-syndrome. Doppler examination protocols however differ because no standard technique has been established so far.[19]
Liver surface assessment using ultrasound showed reasonable diagnostic precision in studies that confirmed good research practice. Further procedures however have proven variable or mild to moderate diagnostic accuracy. In our study, we have tried hepatic venous resistive index measurements through

color Doppler analysis for noninvasive detection of fibrosis. If diagnostic accuracy of this technique could be proved, this would be very beneficial for the patients as it is a readily available, non-invasive, and cost-effective technique for the diagnosis of liver fibrosis and it can help the treating physicians in timely management of these patients.

Seventy-five (n=75) patients with hepatitis B aged between I 8-50 years were enrolled. Data showed Sensitivity, specificity, PPV, NPV, and accuracy were found to be 77.7%, 96.7%, 97.2%, 74.3%, and 85.3% respectively, which is the same as compared to a study done by Lutz HH et al. who compared Doppler ultrasound of hepatic veins with liver histology and transient elastography (TE). Iwao T, et al also concluded that in advanced liver fibrosis, phasicity of hepatic veins dampens, and ultimately it may lead to the reduced caliber and non-visualization of hepatic veins.

In a study conducted by Abbattis T, et al on contrast-enhanced ultrasound assessment of hepatic veins he concluded that Qontrast-calculated TTP was considerably shorter in cirrhotic cases (vs non-cirrhotics and healthy subjects) (71.0 ± 11.3s vs 82.4 ± 15.6s, 86.3 ± 20.3s, $P<0.05$) when the sample was placed in the main hepatic vein.

MA Azizah et al also conducted a study to see the association of hepatic venous waveform with liver cirrhosis and their study also demonstrated that HV spectral waveform was changed in cirrhotic subjects. 11 of 56 cirrhotic showed dampening of hepatic vein Doppler spectral waveform. They noticed the incidence of flattening of HV waveforms correlates with the severity of cirrhosis and there are chances of observing venous outflow hindrance in patients with advanced cirrhosis.

They concluded that this increased stiffness of hepatic parenchyma leads to loss of plasticity in hepatic veins due to impairment of hepatic venous compliance and this incidence of the flattened waveform was associated with the severity of cirrhosis. Venous waveform dampening is more frequently seen in cirrhosis.[20] Similar results are seen in our study. Figures 1 and 2 showing the dampening of venous waveform with the advancement in the stage of fibrosis.
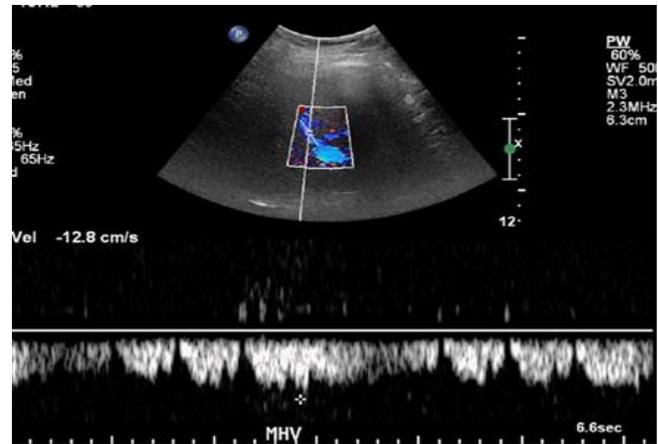

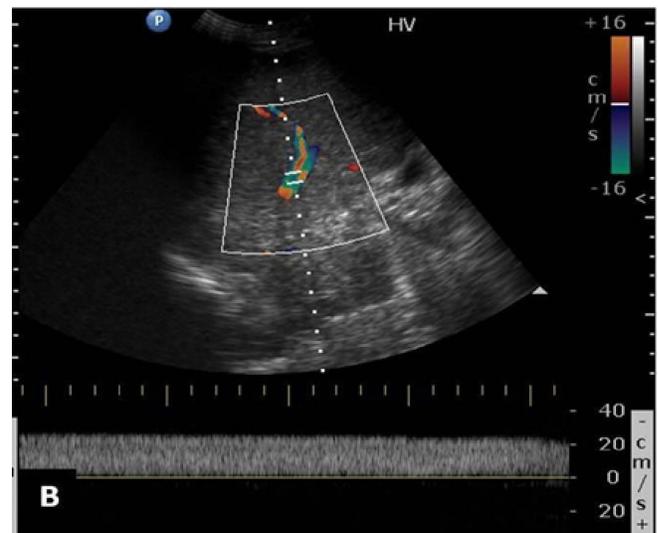**Figure 1: Biphasic waveform in a patient with liver cirrhosis**

Figure 2: Monophasic waveform in advanced cirrhosis

Reports published in the literature to date and the results of this study showed its encouraging potential role in the detection of liver fibrosis.

Conclusion

Hepatic vein resistive index is a reliable noninvasive method in the detection of patients with liver fibrosis and can detect liver fibrosis in patients of CLD with overall sensitivity, specificity, PPV, NPV, and accuracy of 77.7%, 96.7%, 97.2%, 74.3%, and 85.3% respectively.

References

1. Kim MY, Jeong WK, Baik SK. Invasive and non-invasive diagnosis of cirrhosis and portal hypertension. World Journal of Gastroenterology: WJG. 2014 Apr 21; 20(15):4300. DOI: 10.3748/wjg.v20.i15.4300.

2. Siddiqui EH, Shah N, Siddiqui S. Ultrasound; Evaluation of hepatobiliary system. Professional Med J. 2012; 19:187-92.

3. Lefton HB, Rosa A, Cohen M. Diagnosis and epidemiology of cirrhosis. Med Clin North Am. 2009 Jul; 93(4):787-99, vii. DOI: 10.1016/j.mcna.2009.03.002. PMID: 19577114.

4. Iwaisako, K., Brenner, D. A., & Kisseleva, T. (2012). What's new in liver fibrosis? The origin of myofibroblasts in liver fibrosis. Journal of gastroenterology and hepatology, 27 Suppl 2(Suppl 2), 65–68. DOI: 10.1111/j.1440-1746.2011.07002.x.

5. Novo E, Cannito S, Paternostro C, Bocca C, Miglietta A, Parola M. Cellular and molecular mechanisms in liver fibrogenesis. Archives of biochemistry and biophysics. 2014 Apr 15;548:20-37. DOI: 10.1016/j.abb.2014.02.015

6. Friedman SL. Molecular regulation of hepatic fibrosis, an integrated cellular response to tissue injury. Journal of Biological Chemistry. 2000 Jan 28; 275(4):2247-50. DOI: 10.1074/jbc.275.4.2247

7. Mallat A, Lotersztajn S. Cellular mechanisms of tissue fibrosis. 5. Novel insights into liver fibrosis. American Journal of Physiology-Cell Physiology. 2013 Oct 15; 305(8):C789-99. DOI: https://doi.org/10.1152/ajpcell.00230.2013

8. MacLachlan JH, Cowie BC. Hepatitis B virus epidemiology. Cold Spring Harb Perspect Med. 2015 May 1; 5(5):a021410. DOI: 10.1101/cshperspect.a021410. PMID: 25934461; PMCID: PMC4448582.

9. Hamed MA, Ali SA. Non-viral factors contributing to hepatocellular carcinoma. World Journal of Hepatology. 2013 Jun 27;5(6):311. DOI: 10.4254/wjh.v5.i6.311

10. Montuclard C, Hamza S, Rollot F, Evrard P, Faivre J, Hillon P, et al. Causes of death in people with chronic HBV infection: a population-based cohort study. Journal of hepatology. 2015 Jun 1;62(6):1265-71. DOI: 10.1016/j.jhep.2015.01.020

11. Ramos-Lopez O, Martinez-Lopez E, Roman S, Fierro NA, Panduro A. Genetic, metabolic and environmental factors involved in the development of liver cirrhosis in Mexico. World journal of gastroenterology. 2015 Nov 7;21(41):11552. DOI: 10.3748/wjg.v21.i41.11552

12. Roman S, Ojeda-Granados C, Ramos-Lopez O, Panduro A. Genome-based nutrition: An intervention strategy for the prevention and treatment of obesity and nonalcoholic steatohepatitis. World Journal of Gastroenterology: WJG. 2015 Mar 28;21(12):3449. DOI: 10.3748/wjg.v21.i12.3449

13. Aceves D, Ruiz B, Nuño P, Roman S, Zepeda E, Panduro A. Heterogeneity of apolipoprotein E polymorphism in different Mexican populations. Human biology. 2006 Feb;78(1):65-75. DOI: https://doi.org/10.1353/hub.2006.0021

14. Ignee A, Gebel M, Caspary WF, Dietrich CF. Doppler imaging of hepatic vessels-review. Zeitschrift fur Gastroenterologie. 2002 Jan 1; 40(1):21-32. DOI: 10.1055/s-2002-19633

15. Allan R, Thoirs K, Phillips M. Accuracy of ultrasound to identify chronic liver disease. World journal of gastroenterology: WJG. 2010 Jul 28; 16(28):3510. DOI: 10.3748/wjg.v16.i28.3510

16. 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. 2012 Aug 1; 57(8):2222-30. DOI: https://doi.org/10.1007/s10620-012-2153-0

17. Iwao T, Toyonaga M, Oho K, Tanama C, Masumoto H, Sakai T et al. Value of Doppler ultrasound parameters of portal vein and hepatic artery in the diagnosis of cirrhosis and portal hypertension. American Journal of Gastroenterology. 1997 Jun 1; 92(6).

18. Abbattista T, Ridolfi F, Ciabattoni E, Marini F, Bendia E, Brunelli E et al. Diagnosis of liver cirrhosis by transit-time analysis at contrast-enhanced ultrasonography. La radiologia medica. 2008 Sep 1; 113(6):860-74. DOI: https://doi.org/10.1007/s11547-008-0292-3.

19. Tang A, Kim TK, Heathcote J, Guindi M, Jang HJ, Karshafian R, Burns PN, Wilson SR. Does hepatic vein transit time performed with contrast-enhanced ultrasound predict the severity of hepatic fibrosis?. Ultrasound in medicine & biology. 2011 Dec 1; 37(12):1963-9. DOI: 10.1016/j.ultrasmedbio.2011.09.010

20. Kamal MM, Niazi M, Umar M. Sensitivity and Specificity of Ultrasonography in the Early Diagnosis of Liver Fibrosis Stage in Patients with Chronic Liver Disease. Ann Pak Inst Med Sci. 2009; 5: 237-41.