ORIGINAL ARTICLE

TO EVALUATE PATTERNS OF DOPPLER WAVEFORM OF HEPATIC VEINS IN EARLY DETECTION OF CIRRHOSIS IN HCV POSITIVE PATIENTS

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ABSTRACT

INTRODUCTION: In patients with well-compensated liver disease, flattening of the Doppler hepatic vein waveform is suggestive of cirrhosis. It is a cheap and non-invasive modality for the diagnosis of cirrhosis. **OBJECTIVE:** To evaluate patterns of doppler waveform of hepatic veins to help in early detection of cirrhosis in HCV positive patients. **STUDY DESIGN:** Cross-sectional prospective study. **SETTING:** Study was conducted in Imaging Unit of Radiology Department, Liaquat National Hospital (LNH). **DURATION OF STUDY:** 6 months **SUBJECTS AND METHODS:** All patients between 20 - 60 years of age, of either gender having HCV for more than six months confirmed on presence of anti-HCV antibodies on enzyme-linked immunosorbent assay (ELISA) were included. Duplex sonographic examination of the hepatic veins was performed and findings were documented on the structured proforma. **RESULTS:** Mean age of the patients was 49.98 –13.57 years. Majority of the patients (n=146, 61.3%) were males while 92 (38.7%) were females. On doppler waveform, cirrhosis was detected in 114 (47.9%) of all the patients presenting with hepatitis C. **CONCLUSION:** The Doppler wave form pattern of hepatic veins was found to be of cirrhotic pattern in almost half of the patients who had Hepatitis C.

Keywords: Doppler wave form, Hepatic veins, Cirrhosis, HCV

Introduction

Hepatitis C is a significant public health problem in both developed and developing countries.[1] Globally it has been estimated that around 2.8% equating to over 180 million people are infected with hepatitis C virus (HCV).[2] It has been estimated that globally, there are approximately 54,000 deaths and approximately 955,000 disability adjusted life years (DALYs) associated with acute HCV infection.[3] In Pakistan the average estimated prevalence rate has been reported as 4.95% in general adult population, a higher rate compared globally.[4] A significant number of HCV infected patients develops cirrhosis or liver cancer. A study reported cirrhosis prevalence of 13.5% in HCV positive patients.[5]

Though biopsy for histopathological examination remains the gold standard for the diagnosis of cirrhosis, but the clinicians have looked into other less invasive diagnostic modality which is cheap, less invasive and of high quality.[6] The Doppler ultrasonography is considered a suitable alternative. Doppler ultrasonography is a non-invasive and inexpensive modality without radiation hazard which can be used for diagnosis and follow up of patients with chronic liver disease.[7] The Doppler waveform of the hepatic vein in healthy subjects is normally triphasic (two negative waves and one positive wave) because of

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central venous pressure variations during the cardiac cycle.[6] It was hypothesized that the normal triphasic hepatic vein waveform is transformed into a biphasic or monophasic waveform in patients with acute viral hepatitis and cirrhosis due to loss of compliance in walls of the hepatic veins and stiffness of the liver parenchyma.[6-8]

Evidence in the literature has reported a variable diagnosis accuracy of Doppler waveform. A study that recruited 152 patients from age 20-50 years has reported a reasonably good diagnosis accuracy of 88.15%, sensitivity (75.6%), specificity (92.8%), positive predictive value as (79.5%) and negative predictive values as (91.15%).[9] Another study reported the diagnosis accuracy of 77% with abnormal hepatic vein waveforms were detected in 12 of 16 patients with cirrhosis and in eight of 36 patients without cirrhosis.[10]

In another local study there was 79%, sensitivity 86%, specificity 61%, PPV 83% and NPV 67% of Doppler waveform in detection of cirrhosis in HCV positive patients.[11]

There is a limited data available showing positive hepatitis C cases with a doppler waveform suggestive of cirrhosis.[9-10] Moreover, majority of studies conducted were in developed countries, with limited sample size. Therefore, the study is planned to evaluate patterns of doppler waveform of hepatic veins in early detection of cirrhosis in HCV positive patients as Doppler ultrasonography is a rapid cheaper and widely available modality compared to histopathology which is a relatively costly, less widely available and relatively slow. The findings of the study might be useful in identifying the role of Doppler waveform to effectively use it as a diagnostic tool which will help in earlier and easier diagnosis and thereafter management of the patients.

Duplex Doppler Display of the Hepatic Vein

There are many components found on the duplex Doppler display. The two-dimensional display is composed of a gray-scale B-mode image, usually with color Doppler overlay. Convention dictates that flow toward the transducer is depicted in red and flow away from the transducer is in blue; thus, the normal hepatic veins, which head posteriorly toward the retrohepatic IVC, are depicted in blue. (The color scheme convention should always be confirmed on the color bar of the display, as the color scheme can easily be reversed with an inadvertent push of the invert button.) A Doppler gate is then placed over the sample volume within the vessel that the sonographer wants to interrogate, to generate a spectral Doppler tracing. The bottom portion of the duplex display has the spectral Doppler tracing, where the magnitude of flow velocity is plotted against time. According to convention, flow above the baseline indicates flow toward the transducer and flow below the baseline indicates flow away from the transducer. (This relationship can also be instantly reversed by pressing the invert button, which inverts the tracing and places the word Inverted or Inv somewhere on the display. Before interpretation of the tracing, it should be clear whether the spectrum has been inverted.)

Physiology of the Normal Hepatic Vein Waveform

The normal hepatic vein waveform, despite commonly being described as triphasic, has four components: a retrograde A wave, an antegrade S wave, a transitional V wave (which may be antegrade, retrograde, or neutral), and an antegrade D wave.[12] Let us look at how these waves are created by the blood flow through the hepatic veins related to the cardiac cycle. The A wave corresponds to atrial contraction. With the tricuspid valve open, blood is propelled in two directions: antegrade toward the right ventricle and retrograde toward the IVC and into the hepatic veins. At the end of atrial systole, peak retrograde velocity away from the heart is achieved. As ventricular systole commences, the tricuspid valve closes and the retrograde velocity toward the hepatic veins begins to decrease and approach the baseline. There is conflicting literature as to whether a normal hepatic vein A wave must be retrograde with the spectral tracing peaking above the baseline.

Bolondi et al[13] reported that the A wave must be retrograde in normal patients, whereas Pedersen et al[14] showed that an A wave that remains below the baseline may also be found in normal people. During ventricular systole, not only do the ventricular walls contract to propel blood into the right ventricular outflow tract, but there is also movement of the tricuspid valve annulus toward the cardiac apex. These actions create a relative negative pressure in the atrium, causing antegrade blood flow out of the liver and into the heart during the S wave. In the normal heart, the largest amount of antegrade blood flow is during this phase.[15]

The V wave corresponds to atrial overfilling. As the ventricular contraction becomes less intense and the closed tricuspid valve begins to return to its original position, the atrium fills and blood flow velocity toward the heart decreases. The peak of the V wave may be below, at, or above the baseline, depending on whether there is antegrade flow throughout, transient equilibrium with no flow, or transient retrograde flow, respectively. Note that the term triphasic does not include the V wave, perhaps because this wave represents only a transitional phase. The D wave begins as the tricuspid valve opens. During cardiac diastole, the right atrium and ventricle fill passively, with antegrade flow of blood from the liver into the heart. In the normal patient, the velocity of this passive flow is almost always lower in magnitude than the velocity during the S wave. A normal variant, termed the C wave, can cause a small retrograde spike following the A wave.[14-15] As atrial systole ends and ventricular systole commences, the tricuspid valve closes. The tricuspid annulus begins to move toward the cardiac apex and the retrograde velocity of flow toward the liver begins to decrease. However, before the pulmonic valve opens, the pressure in the ventricle increases with continuing contraction of the ventricle, causing a transient bulging of the tricuspid valve into the right atrium. This bulging creates a momentary retrograde pulse toward the liver, causing the C wave. When the pulmonic valve opens and blood is ejected from the right ventricle into the pulmonary outflow tract, the bulge in the tricuspid valve is relieved. Flow into the heart then resumes as usual during the S wave.

Material and Methods

STUDY DESIGN

Descriptive Cross-sectional study.

SETTING

Study was conducted in Imaging Unit of Radiology Department, Liaquat National Hospital (LNH).

DURATION OF STUDY

6 months

SAMPLE SIZE

The sample size is calculated using the WHO sample size calculator for the diagnostic study. The reference study9 values of sensitivity of Doppler ultrasonography 75.61%, specificity of Doppler ultrasonography (92.79%), and prevalence of Cirrhosis among hepatitis C patients as 61.05%, the sample size is estimated. At 95% confidence interval the sample size is calculated as 238. Thus, a minimum of 238 was recruited in this study. Further sample size cannot be increased due to limitation (time constrain).

SAMPLING TECHNIQUE

Non-probability consecutive sampling

SAMPLE SELECTION

Inclusion Criteria

Following patients was invited to participate in this study and was included

- Patients who are HCV positive for more than six months confirmed on presence of anti-HCV antibodies on enzyme-linked immunosorbent assay (ELISA).
- Adults between 20 60 years of age
- Patients of either gender male and female.
- Patients consented for liver biopsy.

Exclusion Criteria

Following patients was excluded from the study.

- Patients with decompensated liver disease or ascites confirmed on history and clinical examination.
- Patients with history of chronic liver disease.
- Patients with history of hepatocellular carcinoma.
- Patients with history of hypertension and ischemic heart disease
- Patients having previous liver biopsy
- Patients having previous Doppler ultrasonography

All the above factors are effect modifiers/confounders and affected the outcome so excluded.

DATA COLLECTION PROCEDURE

After informed consent, 238 patients who are HCV positive was included in the study. The selected patients were subjected to the Doppler ultrasonograpic examination of hepatic veins.

Technique

Ultrasonographic (US) images were primarily acquired on TOSHIBA Nemio 20 with a convex 3.5-MHz probe. Appropriate acoustic windows were used to image the hepatic veins by using intercostal, subcostal, or transabdominal approaches.[20] Gray-scale B-mode evaluation of the liver was first performed, followed by color and spectral Doppler evaluation. Doppler parameters were optimized by following the principles and techniques described in excellent reviews by Kruskal et al.[16-17] and Rubin. All patients enrolled in the study was examined in supine position after overnight fasting. Duplex sonographic examination of the hepatic veins was performed. For this purpose, flow in right, middle and left hepatic veins was observed at a distance of 3-6 cm away from IVC with an angle of 60 degree both with intercostal and subcostal approaches. Measurements was done using mid inspiration and normal breathing in supine or 30 degree left lateral position. At least 4-6 sec of the trace was recorded at the end of non-forced expiration.[9]

Single consultant radiologist having 2 or more years of experience reported both the Doppler ultrasonographic findings. Data were collected on structured proforma for age, gender, wave form pattern of hepatic veins and cirrhosis.

ETHICAL CONSIDERATIONS

The study was conducted according to the ethical guidelines of Helenski declaration and Pakistan Medical research Council (PMRC). Anonymity and confidentiality of participant s data was maintained throughout the research. Informed consent was obtained from all the study participants prior to recruiting in the study.

DATA ANALYSIS PROCEDURE

Data collected was entered and analyzed in the SPSS version 21 and using 2x2 table. Mean with standard deviation was calculated for quantitative variables like age and duration of Hepatitis C. Frequency and percentage was calculated for gender, wave form pattern of hepatic veins and association with cirrhosis were mentioned below. Stratification with respect to age, gender and duration of Hepatitis C was performed and results were formulated.

Results

Mean age of the patients was 49.98 –13.57 years. (Tab.1)

There were 72 (30.3%) patients with ≤50 years and 166 (69.70%) patients with >50 years of age. (Fig.1)

Majority of the patients (n=146, 61.3%) were males while 92 (38.7%) were females. (Fig.2)

Mean duration of hepatitis C was 8.31 – 1.57 months. (Tab.2)

There were 149 (62.6%) patients with ≤8 months and 89 (37.4%) patients with >8 months of duration of hepatitis C. (Fig.3)

On doppler waveform, cirrhosis was detected in 114 (47.9%) (Fig.4 & 5)

Mean	Standard Deviation	Minimum	Maximum
49.98	13.57	25	60

Table 1: Age of the patients, in years (n=238)

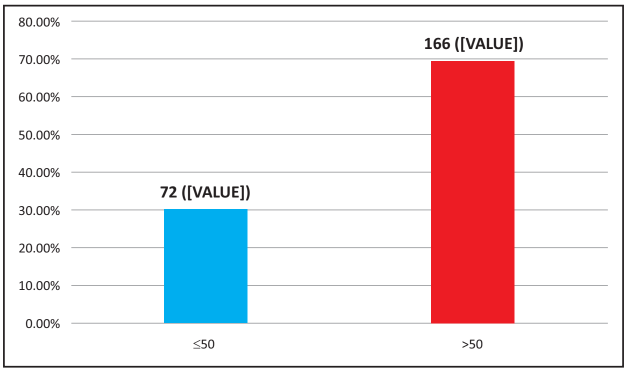

Figure 1: Age group of the patients (n=238)

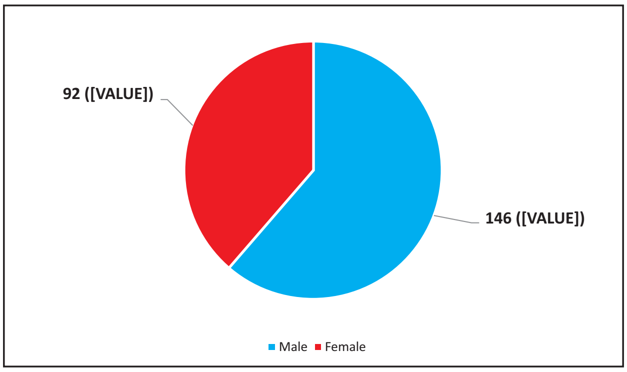

Figure 2: Gender distribution of the patients (n=238)

Mean	Standard Deviation	Minimum	Maximum
8.31	1.57	7	11

Table 2: Duration of Hepatitis C, in months (n=238)

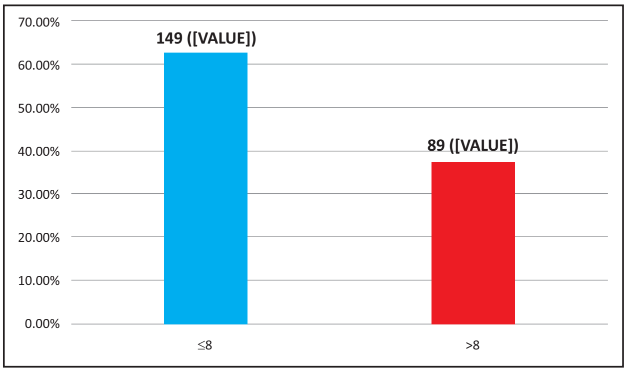

Figure 3: Distribution of duration of hepatitis C, in months (n=238)

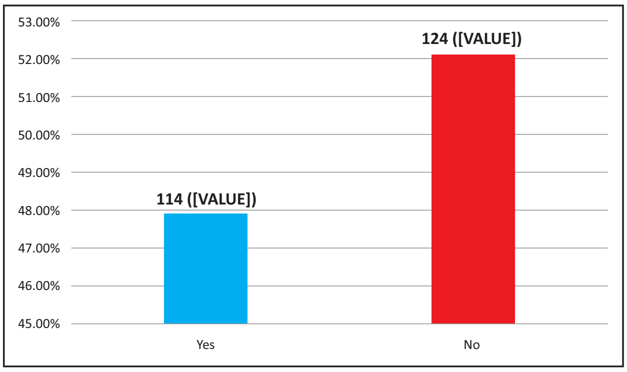

Figure 4: Cirrhosis detected on doppler waveform pattern (n=238)

Cirrhosis detected on Doppler Waveform	Maximum
Yes	114
No	124
Total	**238**

Table 3: Detection of cirrhotic waveform on doppler in Hep C patients (n=238)

Cirrhosis detected on Doppler Waveform	Maximum
Yes	39
No	33
Total	**72**

Table 4: Age ≤50 years detection of cirrhotic waveform on doppler in Hep C patients (n=72)

Cirrhosis detected on Doppler Waveform	Maximum
Yes	75
No	91
Total	**166**

Table 5: Age >50 years & detection of cirrhotic waveform on doppler in Hep C patients (n=166)

Cirrhosis detected on Doppler Waveform	Maximum
Yes	75
No	91
Total	**166**

Table 5: Age >50 years & detection of cirrhotic waveform on doppler in Hep C patients (n=166)

Cirrhosis detected on Doppler Waveform	Maximum
Yes	74
No	72
Total	**146**

Table 6: Male gender& detection of cirrhotic waveform on doppler in Hep C patients (n=146)

Cirrhosis detected on Doppler Waveform	Maximum
Yes	40
No	52
Total	**92**

Table 7: Female gender & detection of cirrhotic waveform on doppler in Hep C patients (n=92)

Cirrhosis detected on Doppler Waveform	Maximum
Yes	70
No	79
Total	**149**

Table 8: Duration of hepatitis C =8 months & detection of cirrhotic waveform on doppler in Hep C patients (n=149)

Cirrhosis detected on Doppler Waveform	Maximum
Yes	44
No	45
Total	**89**

Table 9: Duration of hepatitis C >8 months and detection of cirrhotic waveform on doppler in Hep C patients (n=89)

Discussion

The finding of this study has reported the pattern and use of doppler waveform in detection of cirrhosis in patients with hepatitis C. These findings matched with the findings reported in the literature which has reported a variable number of patients with cirrhotic pattern of Doppler waveform in patients with hep C. A study that recruited 152 patients from age 20-50 years has reported a reasonably good diagnosis accuracy of 88.15%, sensitivity (75.6%), specificity (92.8%), positive predictive value as (79.5%) and negative predictive values as (91.15%).9 Another study reported the diagnosis accuracy of 77% with abnormal hepatic vein waveforms were detected in 12 of 16 patients with cirrhosis and in eight of 36 patients without cirrhosis.[10]

In another local study there was 79%, sensitivity 86%, specificity 61%, PPV 83% and NPV 67% of Doppler waveform in detection of cirrhosis in HCV positive patients based upon histopathology as gold standard.[11]

Doppler ultrasonography is a non-invasive and inexpensive modality without radiation hazard which can be used for diagnosis and follow up of patients with chronic liver disease.[7] The Doppler waveform of the hepatic vein in healthy subjects is normally triphasic (two negative waves and one positive wave) because of central venous pressure variations during the cardiac cycle.[6] It was hypothesized that the normal triphasic hepatic vein waveform is transformed into a biphasic or monophasic waveform in patients with acute viral hepatitis and cirrhosis due to loss of compliance in walls of the hepatic veins and stiffness of the liver parenchyma.[6-8]

Hepatic vein spectral Doppler waveform analysis has also been used in liver transplants, primarily to evaluate for venous stenosis and acute graft rejection. Abnormalities in the spectral Doppler waveform pattern are generally nonspecific. The value of this analysis is that when a normal spectral wave pattern is demonstrated, the clinician can be reassured of a low probability of complications. In the evaluation of hepatic vein stenosis, Choi et al[18] in his study used intraoperative Doppler US to diagnose hepatic vein stenosis with a sensitivity and specificity of 80% and 82%, respectively. Most important, the presence of a triphasic waveform had a 98% negative predictive value for hepatic vein stenosis.

In a study that evaluated hepatic vein stenosis after surgery (range, 1 433 days), Ko et al[19] concluded that a persistent triphasic hepatic vein waveform virtually excluded hepatic vein stenosis. On the other hand, a blunted waveform was found to be nonspecific. It may be seen transiently with postoperative graft edema, which resolves spontaneously. There have been three studies evaluating the usefulness of hepatic vein spectral Doppler waveform analysis to exclude acute rejection.

One study found that during up to 4 years of follow-up, a persistently triphasic waveform had a 92% negative predictive value for acute rejection.

Slightly lower negative predictive values were reported by Britton et aland Zalasin et al,[20-21] who each found that a triphasic waveform had an 84% negative predictive value for acute rejection. Cases of rejection with normal spectral waveforms can perhaps be explained as representing early or mild forms of rejection, where significant graft edema has not set in. Loss of a triphasic waveform was found to be nonspecific for rejection, because conditions such as cholangitis, hepatitis, fibrosis, lymphoproliferative disorder, and juxtahepatic fluid collections were also causes of Doppler waveform blunting.

In short, the clinicians have looked into Doppler ultrasonography as a less invasive diagnostic modality which is cheap, less invasive and of high quality[6] and is a suitable alternative.

Conclusion

The Doppler wave form pattern of hepatic veins was found to be of cirrhotic pattern in almost half of the patients who had Hepatitis C.

Conflict of Interest: Declared None

References

1. Kim WR. Global epidemiology and burden of hepatitis C. Microbes Infect 2002;4(12):1219-25.

2. Chak E, Talal AH, Sherman KE, Schiff ER, Saab S. Hepatitis C virus infection in USA: an estimate of true prevalence. Liver Int 2011; **31(8):** 1090-101.

3. Perz JF, Armstrong GL, Farrington LA, Hutin YJF, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol 2006; **45(4):** 529-38.

4. Waheed Y, Shafi T, Safi SZ, Qadri I. Hepatitis C virus in Pakistan: a systematic review of prevalence, genotypes and risk factors. World J Gastroenterol 2009; **15(45):** 5647-53.

5. Raja NS, Janjua KA. Epidemiology of hepatitis C virus infection in Pakistan. J Microbiol Immunol Infect 2008; **41(1):** 4-8.

6. Kinjo N, Nagao Y, Akahoshi T, Masahiro K, Hashimoto N, Uehara H, et al. Hepatic vein wave form and splenomegaly predict improvement of prothrombin time after splenectomy in hepatitis C virus-related cirrhotic patients. Hepatol Res 2013; **43(9):** 933-41.

7. Guthrie JD, Sheikh MY, Morrell S, Neal D. A case-control study to compare the likelihood of detecting liver disorders using coincident measures of doppler-derived portal vein pressure gradients, hepatic venous waveforms, and the echogenicity of liver parenchyma. J Diagn Med Sonogr 2012; **28(5):** 211-21.

8. Cosgrove D, Lassau N. Imaging of perfusion using ultrasound. Eur J Nucl Med Mol Imaging 2010; **37(1):** 65-85

9. Ahmed N, Shahid R, Tanveer S, Shafique M, Latif A. To Determine the Diagnostic Accuracy of Doppler Waveform Pattern of Hepatic Veins in Detection of Chronic Liver Disease in hepatitis C patients Keeping Histopathology as gold Standard. Pak J Radiol. 2015; **25(3):** 89-92.

10. Colli A, Cocciolo M, Riva C, Martinez E, Prisco A, Pirola M, et al. Abnormalities of Doppler waveform of the hepatic veins in patients with chronic liver disease: Correlation with histologic findings. Am J Roentgenol 1994; **162(4):** 833-7.

11. A Zwiebel WJ. Sonographic diagnosis of hepatic vascular disorders. Semin Ultrasound CT MR 1995; **16(1):** 34-48.

12. McGahan JP, Goldberg BB, eds. Diagnostic ultrasound: a logical approach. Philadelphia, Pa: Lippincott, 1998; 616.

13. Bolondi L, Li Bassi S, Gaiani S. Liver cirrhosis: changes of Doppler waveform of hepatic veins. Radiology 1991; **178(2):** 513-6.

14. Pedersen JF, Dakhil AZ, Jensen DB, Słndergaard B, Bytzer P. Abnormal hepatic vein Doppler wave form in patients without liver disease. Br J Radiol 2005; **78(927):** 242-4.

15. Abu-Yousef MM. Duplex Doppler sonography of the hepatic vein in tricuspid regurgitation. AJR Am J Roentgenol 1991; **156(1):** 79-83.

16. Kruskal JB, Newman PA, Sammons LG, Kane RA. Optimizing Doppler and color flow US: application to hepatic sonography. RadioGraphics 2004; **24(3):** 657-75.

17. Rubin JM. Spectral Doppler US. RadioGraphics 1994; **14(1):** 139-50.

18. Choi JY, Lee JY, Lee JM. Routine intraoperative Doppler sonography in the evaluation of complications after living-related donor liver transplantation. J Clin Ultrasound 2007; **35(9):** 483-90.

19. Ko EY, Kim TK, Kim PN, Kim AY, Ha HK, Lee MG. Hepatic vein stenosis after living donor liver transplantation: evaluation with Doppler US. Radiology 2003; **229(3):** 806-10.

20. Britton PD, Lomas DJ, Coulden RA, Farman P, Revell S.The role of hepatic vein Doppler in diagnosing acute rejection following paediatric liver transplantation. Clin Radiol 1992; **45(4):** 228-32.

21. Zalasin S, Shapiro RS, Glajchen N, Stancato-Pasik A. Liver transplant rejection: value of hepatic vein Doppler waveform analysis. Abdom Imaging 1998; **23(4):** 427-30. Killi RM. Doppler sonography of the native liver. Eur J Radiol 1999; **32(1):** 21-35.