PREVALENCE OF DIFFERENT SONOGRAPHIC STAGES AMONG NEWLY DIAGNOSED CASES OF CHRONIC HEPATITIS C

Hidayat Ullah, Atiq Ur Rehman, Ayesha Zafar

Armed Forces Institute of Radiology and Imaging/ National University of Medical Sciences (NUMS) Rawalpindi Pakistan

ABSTRACT

Objective: To find the prevalence of different sonographic stages among newly diagnosed cases of chronic hepatitis C.

Study Design: Cross sectional study.

Places and Duration of Study: Armed Forces Institute of Radiology and Imaging Rawalpindi, from June 2014 to December 2015.

Material and Methods: All freshly diagnosed patients of chronic hepatitis C (CHC) with a positive anti-HCV and a positive PCR for HCV were subjected to ultrasound abdomen. The sonographic stage of CHC was decided as per previously defined criteria. Prevalence of each sonographic stage at the time of initial diagnosis was determined. Study population was divided in two groups of 'Early stage CHC' (sonographic stage I, II) and 'Advanced stage CHC' (sonographic stage III, IV, V). Student's t-test was applied to compare the means of the values for different sonographic parameters in the two groups.

Results: The study included 178 patients with male to female ratio of 1.86:1. Mean age was 47.5 ± 12.5 years. Prevalence of sonographic stages I, II, III, IV, Va and Vb in study population was 68% (n=121), 12% (n=21), 9% (n=16), 6% (n=11), 3% (n=5) and 2% (n=4) respectively. 'Early stage CHC' and 'advanced stage CHC' showed statistically significant (*p*-value <0.01) difference between average values of liver size, portal vein caliber, mean portal vein velocity and splenic size.

Conclusion: The prevalence of advanced stage CLD (stage III-V) among newly diagnosed cases of chronic hepatitis C is as high as 20% despite the availability of diagnostic facilities.

Keywords: Cirrhosis, End stage liver disease, Hepatitis C, Hepatitis C antibodies, Ultrasonongraphy.

INTRODUCTION

Hepatitis C Virus (HCV) infection is present all across the globe. It has been an important cause of hepatitis following blood transfusion in the United States and Europe until anti-HCV screening of blood donors was introduced in 1991[1]. According to World Health Organization, HCV infection is present in approximately 3% of the world population where about 170 million people having chronic hepatitis C (CHC) are at risk of eventually having hepatic cirrhosis and/or hepatocellular carcinoma[2-4].

Sievert et al found that countries with high rates of CHC are Egypt (15% of population), Pakistan (4.7% of population) and Taiwan (4.4 % of population)[5]. A local study however suggested a prevalence of 6% in Pakistan where about ten million people were found to be the carriers of this infection[6]. Keeping in view the alarming prevalence of HCV infection in Pakistan, there is a need of awareness both among doctors and general population so that affected cases are diagnosed early and treatment instituted accordingly.

Screening people for anti-HCV antibodies provides an efficient way of diagnosing HCV infection. Positive cases can then undergo a polymerase chain reaction (PCR) test for HCV to confirm the activity of the disease. Liver sonography also provides an easy, readily available and cost effective imaging modality for diagnosing the well established cases and assessing the progress of CHC[7]. Findings on abdominal sonography can also be conveniently

Correspondence: Dr Hidayat Ullah, Classified Radiologist AFIRI Rawalpindi Pakistan *(Email: hidayat781@gmail.com)*
Received: 25 Jul 2016; revised received: 25 Aug 2016; accepted: 29 Aug 2016

used to formulate a sonographic staging system of the disease which can help us decide if the disease has been diagnosed early or late.

This study aimed to find the sonographic stage of CHC at the time of its initial diagnosis and use this information as an insight in to the awareness about the disease among doctors and general population.

The rationale of the study to find the prevalence of different sonographic stages among newly diagnosed cases of chronic hepatitis C.

Table-I: Average liver size, portal vein caliber, mean portal vein velocity and splenic size in different sonographic stages of CHC.

Sonographic stage of CHC	Liver size (cm) Mean ± SD	Portal vein caliber (mm) Mean ± SD	Mean Portal Vein Velocity (cm/sec) Mean ± SD	Spleen size (cm) Mean ± SD
Stage I	13.9 ± 0.6	10.7 ± 0.9	19.7 ± 2.7	10.4 ± 0.6
Stage II	13.6 ± 0.5	11.8 ± 0.8	19.5 ± 2.7	12.2 ± 0.9
Stage III	12.4 ± 0.9	13.8 ± 0.5	11.6 ± 1.3	14.4 ± 0.8
Stage IV	10.3 ± 0.7	14.5 ± 0.6	9.5 ± 1.2	16.8 ± 1.2
Stage Va	11.1 ± 0.8	14.54 ± 0.4	11.2 ± 0.8	16.5 ± 0.5
Stage Vb	10.3 ± 0.3	14.4 ± 0.4	10 ± 0.8	17.3 ± 0.9

Table-II: Comparison of means of average liver size, portal vein caliber, mean portal vein velocity and splenic size in 'early stage CHC' and 'advanced stage CHC'. Values with different small letters are significantly (p<0.01) different from each other.

Sonographic Stage of CHC	Average Liver Size (cm)	Average PV Caliber (mm)	Average Mean PV Velocity (cm/sec)	Average Spleen Size (cm)
Early stage CHC (sonographic stage I, II)	13.9 ± 0.6a	10.9 ± 0.9b	19.7 ± 2.7a	10.7 ± 0.9b
Advanced stage CHC (sonographic stage III, IV, V)	11.3 ± 1.3b	14.2 ± 0.6a	10.7 ± 1.5b	15.7 ± 1.5a
t-value	17.77	20.28	29.09	25.35
p-value	<0.01	<0.01	<0.01	<0.01

PATIENTS AND METHODS

In this cross sectional study, patients were included by a non probability purposive sampling method. Patients of all ages and either gender reporting to Armed Forces Institute of Radiology & Imaging (AFIRI), Rawalpindi for ultrasound abdomen after having a positive anti-HCV test and a positive polymerase chain reaction (PCR) for HCV were included in the study. Previously undiagnosed cases having incidental findings suggestive of chronic liver disease (CLD) on abdominal sonography were also included if they were found reactive for anti-HCV with a positive PCR test. Already known cases of hepatitis C, patients with no or a negative PCR test, those with coexisting hepatitis B infection and unwilling patients were excluded. Normal hepatic parenchyma shows echogenicity equal to or a little greater than that of spleen and renal cortex[8]. Liver has been described to have four sonographic grades with grade 0 depicting normal hepatic echogenicity while grade 1, 2 and 3 representing increasing fatty infiltration resulting in obscured margins of intrahepatic vasculature and the diaphragmatic outline[9]. Patients were excluded if they had grade 2 or more fatty infiltration of liver.

Sample size was calculated by using the following formula.

$$N = \frac{(pq)(Za)^2}{d^2}$$

Where p=Prevalence of sonographically detectable CLD among study population expressed as a percentage; q=100-p; Za (Z Alpha)=1.96 using standard normal variate tables; and d (relative precision) = 20% of p[10]. A pilot study of 20 cases was carried out to find the approximate prevalence of sonographically detectable CLD among the study population.

This revealed 7 cases having sonographically detectable CLD at the time of initial diagnosis of HCV infection giving a value of 35% for *p* to calculate the minimum sample size of 178.

After an informed consent for inclusion in the study, ultrasound abdomen was carried out by a radiologist. All patients were scanned by the same radiologist using a 3.5 MHz convex transducer using Toshiba Nemio machine with measurement was made mid way between the formation of main portal vein and its bifurcation. The sample gate was kept open to include half to 2/3rd of the portal vein lumen with Doppler angle being always kept <60. Spectral analysis was done for 2-3 cycles and average of the mean portal vein velocity was recorded[11].

During ultrasonography following criteria were used to grade liver disease. Liver Grade 0

Table-III: Sonographic staging of chronic liver disease.

Sonographic Stage of CLD	Terminology	Sonographic findings	
Stage I	No sonographic Chronic Liver Disease (NS-CLD)	Liver	Fine texture, smooth surface, sharp edge
		Portal vein	Calibre <13mm, hepatopetal velocity ≥15 cm/sec
		Spleen	Size <12 cm, no splenic varices
		Ascites and/or pleural effusion	Nil
Stage II	Chronic Liver Disease (CLD)	Liver	Coarse texture, ± irregular surface, ± blunted edge
		Portal vein	Calibre <13mm, hepatopetal velocity ≥15 cm/sec
		Spleen	Normal size/enlarged, no splenic varices
		Ascites and/or pleural effusion	Nil
Stage III	CLD with Portal Hypertension (CLD-PH)	Liver	As in stage II
		Portal vein	Calibre >13mm, hepatopetal velocity <15 cm/sec or flow reversal
		Spleen	Size >12 cm, ± splenic varices
		Ascites and/or pleural effusion	Nil
Stage IV	Decompensated Cirrhosis (DC)	Liver	As in stage II
		Portal vein	Calibre >13mm, hepatopetal velocity <15 cm/sec or flow reversal
		Spleen	Size >12 cm, + splenic varices
		Ascites and/or pleural effusion	Present
Stage Va	Stage II/III with HCC	Stage II/III with hepatic space occupying lesion suggestive of HCC	
Stage Vb	Stage IV with HCC	Stage IV with hepatic space occupying lesion suggestive of HCC	

Doppler facility. Same protocol was used for Doppler evaluation of portal vein to ensure standardization. Scanning was done during quite inspiration after overnight fasting. The probe was aligned along the long axis of the portal vein and (Normal liver): Homogeneously fine echotexture, smooth surface; sharp edge; portal vein caliber <13 mm with hepatopetal velocity of ≥15 cm/sec[12-14]. Liver Grade 1 (chronic liver disease): coarse echotexture, ± irregular surface, ± blunt or

rounded margin, portal vein caliber <13 mm with hepatopetal velocity of ≥15 cm/sec. Liver Grade 2 (CLD with portal hypertension): coarse echotexture, ± irregular surface, ± blunt or rounded margin with portal vein caliber >13 mm and a hepatopetal velocity of <15 cm/sec or a hepatofugal flow. Liver Grade 3 (CLD with HCC): liver grade 1 or 2 with space occupying lesion/lesions suggestive of hepatocellular carcinoma. Spleen was graded as spleen grade 0: length <12cm, no varices; spleen grade 1: length >12 cm, no varices; spleen grade 2: length >12 cm with varices[15]. Note was made for presence of ascites and/or pleural effusion. Based on these ultrasound findings, a sonographic stage of hepatitis C infection was decided as follows. Stage I: liver grade 0, spleen grade 0, no ascites or pleural effusion; Stage II: liver grade 1, spleen grade 0 or 1, no ascites or pleural effusion; Stage III: liver grade 2, splenic grade 1 or 2, no ascites or pleural effusion; Stage IV: liver grade 2, spleen grade 1 or 2, with ascites and/or pleural effusion; Stage Va: liver grade 3, spleen grade 1 or 2, no ascites and/or pleural effusion; Stage Vb: liver grade 3, splenic grade 1 or 2, with ascites and/or pleural effusion.

Findings were recorded on an already prepared proforma. Data were analyzed by SPSS 21. Prevalence of different sonographic stages of CHC among study population was calculated. Average liver size, portal vein caliber, mean portal vein velocity and splenic size were determined. Study population was divided in two groups of 'Early stage CHC' (sonographic stage I, II) and 'Advanced stage CHC' (sonographic stage III, IV, V). Student's t-test was applied to compare the means of the values for different sonographic parameters in the two groups[16]. A *p*-value of less than 0.05 was considered as significent value.

RESULTS

A total of 178 patients were included in the study. Out of them, 65% (n=116) were males while 35% (n=62) were females. Male to female ratio was 1.86:1. The mean age was 47.5 ± 12.5 years. The age distribution curve showed non-zero (positive) skewness (fig-1).

Stage I disease was found in 68% (n=121) while stage II disease was noted in 12% (n=21). Stage III disease was present in 9% (n=16) and stage IV CLD was detected in 6% (n=11) of patients. Stage Va was shown by 3% (n=5) and stage Vb was noted in 2% (n=4).

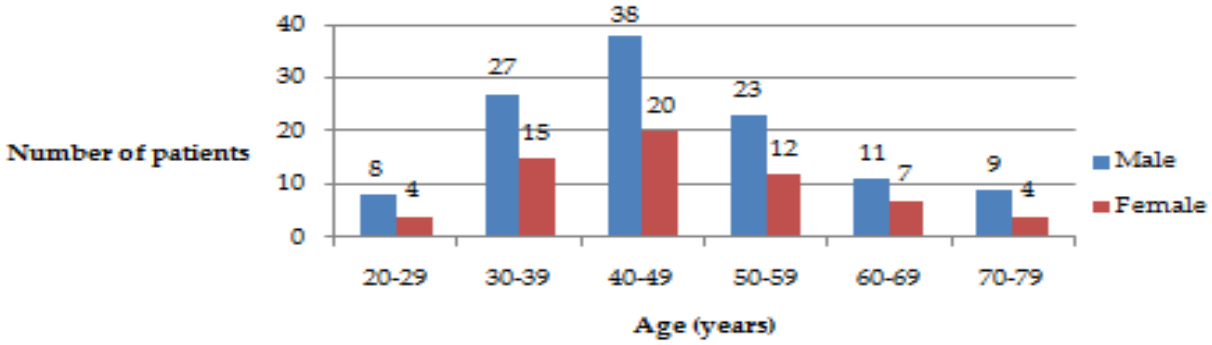

Figure-1: Age distribution curve of study population with positive skewness.

Table-I shows liver size, portal vein caliber, mean portal vein velocity and splenic size in different stages of hepatitis C with progressive change in the values of these variables as the disease advances in its sonographic stage. In 'Early stage CHC' the average liver size, average portal vein caliber, average mean portal vein velocity and average spleen size were 13.9 ± 0.6 cm, 10.9 ± 0.9 mm, 19.7 ± 2.7 cm/sec and 10.7 ± 0.9 cm respectively. In 'Advanced stage CHC', these values were 11.3 ± 1.3 cm, 14.2 ± 0.6 mm, 10.7 ± 1.5 cm/sec and 15.7 ± 1.5 cm respectively

with statistically significant (*p*-value <0.01) difference between the two groups (table-II and fig-2).

DISCUSSION

Chronic hepatitis C is an important cause of morbidity and mortality all across the globe especially in the developing world. In Pakistan the overall prevalence of seropositivity for hepatitis C in general population is as high as 6% with about ten million people having HCV infection[6]. Some studies, however, suggest a lower prevalence of 3% in Pakistan which might be because of difference in the sample population[17]. Ultrasound plays an important role in the evaluation of such patients and detects the possible complications[18].

There have been several models of classification and staging of CHC, some of which focus on the end stage liver disease for selecting patients for liver transplant[19]. Others focus on histopathological evaluation of hepatic inflammation and fibrosis for staging of the disease[20,21]. Our study introduced a staging model taking in to account the sonographic appearance of liver, portal vein and spleen along with the presence of ascites, pleural effusion and hepatocellular carcinoma. Ribeiro et al suggested a somewhat similar staging system but that was based on multimodal data[22]. The strength of the proposed staging model is coupling simple hepatic and splenic sonographic grades with other sonographic features making categorization of CLD possible. This sonographic staging model can be used for any chronic infection of liver including CHC and, if adopted by radiologists, is likely to make ultrasound reports in CLD patients more standardized and structured. Table-III outlines the salient features of the sonographic staging model for CLD used in this study.

Many cases of CHC go undetected till late because the disease is asymptomatic. Such cases are diagnosed only when the disease is complicated by portal hypertension, hepatic cirrhosis and hepatocellular carcinoma. Moorman et al in their chronic hepatitis Cohort Study (CHeCS) showed that 17% cases qualified for having a 'late diagnosis' despite having access to health care system[23]. Our study confirmed this finding in our set up where 20% cases presented in advanced stages of the disease (sonographic stage III, IV, V) at the time of initial diagnosis while 80% of cases were diagnosed in early stages (sonographic stage I, II). The high prevalence of 'late diagnosis' is alarming because it increases the morbidity and mortality associated with the disease. A high index of suspicion is necessary for early diagnosis of infected patients/carriers to avoid complications and to reduce the spread of disease to others by timely institution of therapy. Introduction of mandatory blood screening test on annual basis especially in areas with high prevalence of HCV infected patients can be considered. This will help diagnosing majority of

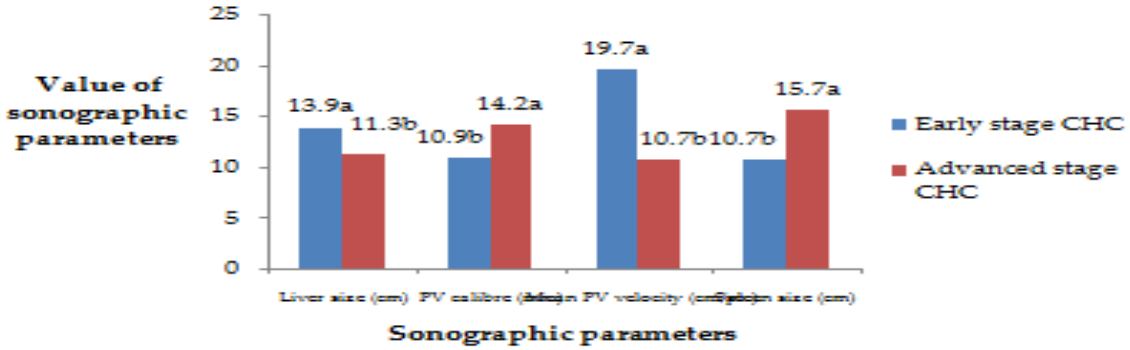

Figure-2: Comparison of means of average liver size, portal vein caliber, mean portal vein velocity and splenic size in 'early stage CHC' (sonographic stage I, II) and 'advanced stage CHC' (sonographic stage III, IV, V). Values with different small letters are significantly (*p*<0.01) different from each other.

patients in NS-CLD stage of the disease who are more likely to be completely cured by the timely treatment.

Butterfield et al showed that in cases of severe mental illness, the rate of CHC infection in males was almost twice that among females[24]. This was attributed to their increased chances of exposure to the causative factors. In the multivariate model, however, gender was not found to be significantly playing a role in CHC. Our study, on the other hand, also showed that the proportion of seropositive males 65% (n=116) was almost twice the proportion of infected females 35% (n=62). The reasons are likely to be the same as outlined by Butterfield et al including more chances of being exposed to the causative factors. Alternatively less number of females reporting to the healthcare system because of socio economic reasons could also be playing some role. More, population based studies are required to find the representative epidemiologic features of CHC in Pakistan.

Advanced stage CHC has easily recognizable sonographic patterns. Smaller liver size with coarse echotexture, dilated portal vein with reduced mean velocity and occasionally even flow reversal, splenomegaly, the presence of ascites and/ or pleural effusion and presence of hepatic space occupying lesion in cases of hepatocellular carcinoma are the sonographic features which help in determining the stage of CLD. The study confirmed that there was a statistically significant (p-value <0.01) difference between 'Early stage CHC' and 'Advanced stage CHC' in terms of averege liver size, spleen size, portal vein caliber and portal vein folw velocity.

A limitation of this study is that it took into account only those seropositive cases who reported for ultrasound. Thus the sample might not be representative of the actual situation in general population. Larger population based studies are required to assess the situation more accurately and suggest appropriate steps for improvement.

CONCLUSION

Despite the availability of diagnostic facilities, the prevalence of advanced stage CLD (stage III-V) is as high as 20% among the newly diagnosed cases of chronic hepatitis C.

RECOMMENDATIONS

A high index of suspicion among the clinicians and periodic screening of general population can reduce this prevalence by ensuring an early diagnosis. The proposed sonographic staging, if adopted by radiologists, is likely to make ultrasound reports in CLD patients more standardized and structured.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

REFERENCES

1. Van der Poel CL. Hepatitis C virus and blood transfusion: past and present risks. J Hepatol 1999; 31: 101-06.
2. Lavanchy D. The global burden of hepatitis C. Liver International 2009; 29(s1): 74-81.
3. Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: New estimates of age specific antibody to HCV seroprevalence. Hepatology 2013; 57(4): 1333-42.
4. Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. Journal of Hepatology 2006; 45(4): 529-38.
5. Sievert W, Altraif I, Razavi HA, Abdo A, Ahmed EA, AlOmair A, et al. A systematic review of hepatitis C virus epidemiology in Asia, Australia and Egypt. Liver International 2011; 31(s2): 61-80.
6. Raja NS, Janjua KA. Epidemiology of hepatitis C virus infection in Pakistan. Journal of Microbiology Immunology and Infection 2008; 41(1): 4.
7. Najafizadeh M, Karayev Z, Farhadi N. Role of Liver Ultrasound in Diagnostic Process of Hepatitis C Disease: Comparison with Serum inflammatory indices level and t-helper 1 cytokine responses. Research Journal of Biological Sciences 2009; 4(2): 200-03.
8. Singh D, Das C, Baruah M. Imaging of non alcoholic fatty liver disease: A road less travelled. Indian J Endocr Metab 2013; 17(3): 990-95.
9. Saadeh S, Younossi Z, Remer E, Gramlich T, Ong J, Hurley M, et al. The utility of radiological imaging in nonalcoholic fatty liver disease. Gastroenterology 2002; 123: 745-50.
10. Sample size calculation: Cross-sectional studies [Internet]. community medicine 4 asses. 2014 [cited 2016]. Available from: https://communitymedicine4asses.wordpress.com/2014/05/11/sample-size-calculation-cross-sectional-studies.
11. Ulusan S, Yakar T, Koc Z. Evaluation of portal venous velocity with doppler ultrasound in patients with nonalcoholic fatty liver disease. Korean J Radiology 2011; 12(4): 450-55.

12. Goyal N, Jain N, Rachapalli V, Cochlin D, Robinson M. Non-invasive evaluation of liver cirrhosis using ultrasound. Clinical radiology 2009; 64(11): 1056-66.
13. Moriyasu F, Nishida O, Ban N, Nakamura T, Sakai M, Miyake T, et al. " Congestion index" of the portal vein. American Journal of Roentgenology 1986; 146(4): 735-39.
14. Mildenberger P, Lotz R, Kreitner K. [Duplex sonography of the normal portal vein]. Deutsche medizinische Wochenschrift (1946) 1987; 112(50): 1936-39.
15. Goel A. Normal reference values | Radiology Reference Article | Radiopaedia.org [Internet]. Radiopaedia.org. 2016 [cited 2016]. Available from: http://radiopaedia.org/articles/normal-reference-values.
16. T-Test Calculator for 2 Independent Means [Internet]. Socscistatistics.com. 2016 [cited 2016]. Available from: http://www.socscistatistics.com/tests/studentttest/Default2.aspx.
17. Ali SA, Donahue RM, Qureshi H, Vermund SH. Hepatitis B and hepatitis C in Pakistan: prevalence and risk factors. Int J Infect Dis 2009; 13(1): 9-19.
18. Gray-scale ultrasound in hepatic cirrhosis and chronic hepatitis: diagnosis, screening, and intervention. Seminars in Ultrasound, CT and MRI; 2002. Elsevier.
19. Papatheodoridis GV, Cholongitas E, Dimitriadou E, Touloumi G, Sevastianos V, Archimandritis AJ. MELD vs Child-Pugh and creatinine-modified Child-Pugh score for predicting survival in patients with decompensated cirrhosis. World journal of gastroenterology 2005; 11(20): 3099.
20. Batts KP, Ludwig J. An Update on Terminology and Reporting. The American journal of surgical pathology 1995; 19(12): 1409-17.
21. Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. Hepatology 1996; 24(2): 289-93.
22. Ribeiro RT, Marinho RT, Sanches JM. Classification and staging of chronic liver disease from multimodal data. IEEE transactions on biomedical engineering 2013; 60(5): 1336-44.
23. Moorman AC, Xing J, Ko S, Rupp LB, Xu F, Gordon SC, et al. Late diagnosis of hepatitis C virus infection in the Chronic Hepatitis Cohort Study (CHeCS): missed opportunities for intervention. Hepatology 2015; 61(5): 1479-84.
24. Butterfield MI BH, Meador KG. Gender differences in hepatitis C infection and risks among persons with severe mental illness. Psychiatr Serv 2003; 54(6): 848-53.