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Research Article

DIAGNOSTIC ACCURACY OF TRANSIENT ELASTOGRAPHY FOR EARLY DETECTION OF HEPATOCEELULAR CARCINOMA IN VIRAL ETIOLOGY RELATED LIVER CIRRHOSIS

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ABSTRACT

Background: Hepato-cellular Carcinoma (HCC) is a serious disease that is consistently increasing among the population of third world countries. Due to scarcity of tools to detect HCC at an early stage it is resulting in high morbidity and mortality. This study was planned to bring a new method for early diagnosis of HCC.
Objective: To determine the diagnostic accuracy of Transient Elastography for the early detection of HCC in viral etiology related liver cirrhosis keeping Dynamic Computed Tomography as a gold standard.
Methods: This was a cross sectional study carried out for a duration of six months, from 21st September 2015 to 21st March 2016, in Centre for Liver and Digestive Disease (CLD), Medical Unit 1, Holy Family Hospital, (HFH) Rawalpindi, Pakistan. Patients with diagnosis of cirrhosis secondary to HBV and HCV were enrolled for this study irrespective of their age and gender. Detailed history, physical examination and biochemical measurements were recorded. Patients underwent Transient Elastography and Dynamic Triphasic CT scan to see HCC.
Results: Hundred and forty-four patients fulfilling the inclusion criteria were included in this study. There were 79 (54.9%) males and 65 (45.1%) females. The mean ± standard deviation age of study population was 44.01± 10.270 years. On analysis of demographicdata, it was observed that 73 (50.7%) were below 45 years of age & 71 (49.3%) were above 45 years of age. Based on these results, while taking CT scan as the gold standard, the sensitivity of Transient Elastography for diagnosis of HCC was found to be 64.47%, specificity 80.88%, positive predictive value 79.03% and negative predictive value 67.03%. While diagnostic accuracy of test was 72.2%
Conclusion: Our study shows that Transient Elastographycan be used as a simple non-invasive test for early identification of HCC in patients with viral etiology cirrhosis.

INTRODUCTION

Liver fibrosis plays an important role in the development of liver cirrhosis and hepatocellular carcinoma. HCC is the 6th most common cause of cancer worldwide[1], with a prevalence rate of about 5%. Risk of development of hepatocellular carcinoma is between 1% and 5% in hepatitis B and C related cirrhosis respectively[1].HCC is associated with cirrhosis in 80% of the cases[2]. In Pakistan the prevalence of hepatitis C and B is 4.8% and 2.5% respectively.[3] HCV related HCC is seen in 60 to 70% of cases and HBV related HCC is seen in 20% of the cases.[3]

Once cirrhosis develops, risk of development of HCC is 2 to 6% per year in hepatitis B and 2 to 5% in hepatitis C chronic infection.[1] Early detection of tumor increases the chance of prolong survival with the appropriate treatment. Liver biopsy is no longer being used for the screening and early diagnosis of HCC, especially for the tumor which is in curative stage. About 30% of the patients of HCC are the candidate for curative treatment. Therefore, the patients with cirrhosis are the ideal candidates for surveillance. The standard approach for surveillance is measurement of α-fetoprotein level and ultrasound abdomen after every 6 months[2], but sensitivity of α-fetoprotein is very low for detection of HCC and sensitivity of ultrasonography is only 63%, as small nodules can be missed by ultrasonography.[2]In contrast to ultrasonography, Dynamic Computed tomography (CT) has a high sensitivity (100%) and specificity (96%) in diagnosing HCC, however, it cannot be used repeatedly in high risk cirrhotic patient because of radiation exposure and high expense.[4]

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As we know liver fibrosis is an independent risk factor for the development of hepatocellular carcinoma, but with the development of FibroScan using transient elastography, it has become possible to detect and quantify liver fibrosis non-invasively.[5] Transient elastography is an ultrasound-based technique which measures liver stiffness by the difference in the velocity of elastic shear wave propagation across the liver. Increased liver stiffness measured by FibroScan® is associated with higher incidence of hepatic decompensation episodes and with presence of HCC. The Liver Stiffness Measurement (LSM) has a range from 23kPa to 75kPa. The cut off value of ›38.5kPa in cirrhotic patient is an important indicator to evaluate HCC.[6]

Many studies have been done which emphasize on the diagnostic accuracy of transient elastography and serological markers as predictors of HCC individually[5,9,10]. In a recent study by Diana Feier *et al*, the sensitivity and specificity of LSM at ›38.5kPa for the prediction of HCC in a cirrhotic patient is 51.7% and 90.4% respectively.[6]

The rationale of our study was to find out whether the transient elastography which is a non-invasive and easily available technique with no radiation exposure has any role for the early detection of HCC in viral etiology related liver cirrhosis. This technique has a promising role in risk assessment and surveillance of HCC limiting the need of unnecessary and costly investigations.

Experimental Section

Methodology

After seeking ethical approval from Institutional Research Forum of Rawalpindi Medical College and permission from hospital's authorities, a written consent was taken from each and every patient fulfilling the inclusion criteria. Information was collected through reports of the diagnostic tests performed and data was entered in the structured Performa.

A group of patients consisted of 144 cases, who were previously diagnosed with viral etiology related liver cirrhosis were enrolled in this study according to the inclusion criteria. Inclusion criteria was patient of either gender between 18 to 80 years of age, positive anti-HCV antibodies or HBsAg by ELISA for at least 6 months, and patients with ultrasonographic evidence of cirrhosis i.e. overall coarse and heterogeneous echotexture with surface nodularity and reduction in size of the right lobe of the liver, splenomegaly more than11cm in diameter with either no or presence of ascites. All those patients were excluded who have liver cirrhosis with moderate and massive ascites and patients with HCC who had history of RFA, TACE or currently using Sorafenib.

Ultrasound abdomen and Hepatitis B and C serology by ELISA were done for all patients on the same day. Transient Elastography was performed by FibroScan® (502 TOUCH; E300M001.2, version 2) in all the patients for the measurement of LS (liver stiffness) in viral etiology related liver cirrhosis. Liver Stiffness measurements were done in right lobe of the liver after USG abdomen so that focal lesions were not in the acquisition window. FibroScan® is a device that contains 5 MHz ultrasound transducer probe attached to the axis of vibrator. Stiffness of the liver tissue that is directly related to the shear velocity measured by transient elastography and it correlates with liver fibrosis. The cut off mean value will be ›38.5kPa in patient with HCC.

The vibrator generates painless vibration (with a frequency of 50 Hz and amplitude of 2mm) which produces an elastic shear wave across the liver. The velocity of elastic shear wave is directly proportional to the stiffness of the tissue. Transient elastography was performed by two experienced gastroenterologists (at least 250 TE performed by each one). Liver Stiffness measurement was expressed in kPa. The value of liver stiffness of ›38.5kPa measured by FibroScan was suggestive of presence of HCC.

Those patients underwent Dynamic Computed Topography on the same day. Dynamic CT was done via AQUILION RXL 16 slice model machine in the Radiology Department of same hospital. The reporting of CT scan film was performed by an assistant professor Radiology department who had reported more than 500 CT scans. Data analysis was entered and analyzed through Statistical Package of Social Sciences (SPSS version 18). Diagnostic accuracy was calculated for the testing modality.

RESULTS

The mean ± standard deviation age of study population was 44.01± 10.270 years of which 79 (54.9%) males and 65 (45.1%) females.

The results of transient elastography showed 62(43%) patients to have HCC, whereas CT scan diagnosis of HCC was confirmed in 76(52%) patients.

When the results of transient elastography and CT scan were compared, it was found that out of 62 patients that tested positive for HCC on elastography, 49 had CT scan evidence of HCC. Among 82 patients who tested negative for HCC on elastography 27 had HCC on biopsy (p value 0.00). True positive 49, false positive 13, true negative 55, and false negative 27.

Table 1 Diagnostic accuracy of the Transients Elastography Taking CT scan diagnosis of HCC as Gold standard

		CT Scan Diagnosis of HCC	
		YES	**No**
Transient elestrography diagnosed HCC	**YES**	49(64%)	13(19%)
	NO	27(35%)	55(80%)
Sensitivity	Specificity	PPV	NPV
64.4%	80.8%	79.0%	67.0%
Diagnostic Accuracy		72%	

Stratification of age and gender is mentioned in table #2.

Table 2 Impact of Gender and Age in The Diagnosis of The HCC By Transient Elastography

		Transient Electrography Diagnosis of HCC		**P - value**
		Yes	**No**	
Gender	Male	35	44	
	Female	27	38	0.435
Age	Less than 45 years	42	31	
	45 years and above	40	31	0.045

DISCUSSION

Patients with liver cirrhosis have a significantly reduced life expectancy compared to non-cirrhotic patients due to complications such as ascites, bleeding of oesophageal varices, hepatic encephalopathy, hepatorenal or hepatopulmonary syndrome and hepatocellular carcinoma (HCC)[11]. Particularly the increasing incidence of HCC secondary to hepatic cirrhosis contributes significantly to the high mortality seen in these patients[12]. Hence, most guidelines recommend regular screening for HCC in patients with liver cirrhosis at least every six months[13,14]

Liver stiffness measurement using TE is recognized as accurately assessing the stage of liver fibrosis in patients with chronic HCV infection [15,16], recorded values increasing as the liver disease progresses, and the highest LS being specific for cirrhotic patients with associated HCC [17]. Scientists thought that LS measurement which is well known noninvasive tool for assessment of liver fibrosis and cirrhosis can be used for diagnosis of HCC as a screening method. Many studies have been done in this domain. Initial studies reported a cut-off value of 53 kPa as suggestive for the presence of HCC in HCV cirrhotic patients[17], especially if total serum bilirubin was higher than 1.0 mg/dL[18]. However, this proposed threshold was not independently validated, and ranges between 12.5 and 53.7 kPa were used in other reports. [19,18, 20]We used the cut off value of 38.5 kPa in our study. In Foucher's study [17] the 53.7 kPa value was obtained from a subset of only 19 patients with HCC, and the Sensitivity and Specificity were 37% and 87%, respectively, with PPV and NPV of 30% and 90%. In addition, the study population in all mentioned papers was heterogeneous (HBV, HCV and ethanol), whereas our study included only HCV and HBV patients. For all these reasons we chose to determine our own cut off value (38.5 kPa)[11]. LS measured by magnetic resonance elastography can assess the presence or absence of HCC in patients with compensated cirrhosis with mild degree of fibrosis, but it's a very expensive method and practically not possible to perform in every patient. Many studies that have been done and mentioned above did not use any other predicting parameter, in addition to LS. In our study we only use LS measurement as the most important predictor of liver cancer and checked its diagnostic accuracy. Taking into account the cutoff values obtained for LS measurements alone, we can suggest that aLS greater than 38 kPa in an HCV and HBV infected cirrhotic patient is an important indicator to further investigate the presence of a liver tumor. Another important and fascinating parameter used in other studies is the IQR (interquartile range) percentage of LS measurements. Interquartile range represents the interval including 50% of patients above and below the median. According to the study by Diana feier *et al*, the IQR/LS should be less than 30% of the median value [21]. Higher values of IQR percentage is associated with destruction of normal liver architecture, and this destruction can be due to underlying liver tumor. In our study, we have not calculated IQR percentage but we suggest that it should be combined with LS measurement as it increases the sensitivity of transient elastography for the early detection of HCC.

It cannot be explained that HCC increases the LS because of its structure, as it is well known that liver cancer is a softtissue vascular tumor[122]. More probably, it is the deformation stress produced by the chaotic growth of the tumor inside of an already hard medium (the cirrhotic tissue) that induces the LS and the IQR increment. This again supports the hypothesis of Mueller and Sandrin, according to which not only matrix but also pressure-associated conditions influence LS[23]. The inhomogeneous distribution of LS appears to generate a "stiffness shadow", that may have important clinical implications: if a certain patient with HCV cirrhosis, followed up by TE among other methods, suddenly develops an increase in LS median value, as well as in IQR, it may indicate the presence of HCC and may speed up the referral to other diagnostic techniques.

As we already know that high ALT value is stronglyassociated with the presence of HCC[25,26], esophageal varices and the presence of HCC are usually associated with each other and each of them predict a poor outcome of the other[27]. As a common practice, AFP is widely used for HCC diagnosis, despite its low sensitivity and specificity. However, high AFP levels at baseline were associated with an increased risk for HCC in HCV infected patients[28,29]. All the above mentioned parameters except the esophageal varices are the independent predictors of HCC. We also suggest that studies should be made to incorporate these independent predictors along with LS measurement into one study module or score for early detection of HCC in high risk patients.

We have found in our study that liver stiffness of the liver was significantly greater in those with HCC in HCV and HBV group than among cases without HCC. FibroScan has been used worldwide as a non-invasive measurement system for liver fibrosis and HCC concurrence is more frequent in cases with high grade of liver fibrosis on FibroScan.

Sensitivity, Specificity, positive predictive value, negative predictive value, diagnostic accuracy of a predictor should be assessed under ideal conditions, which we tried to reproduce in a case-matching study by assuring a homogeneous "background noise" in the two groups [30]. By trying to generate the same baseline conditions, we also overcame some of the critical aspects of case-control studies: the selection of cases, recall bias, and surveillance bias. Therefore, we only enrolled patients under surveillance according to the latest recommendations[31,32] and with the same frequency. Additionally, we stratified the patients according to age, sex, type of hepatitis infection - because recent reports suggest a direct correlation between these parameters and the presence of HCC[33-36].

The most important finding of the study seems to be the increased LS as a predictor of HCC presence. Since TE is a common examination in outpatient settings, the finding of an elevated LS value (e.g. >38 kPa, as our data suggest) with compensated liver cirrhosis may raise awareness for early HCC and may hasten the referral to imaging techniques. This will not become a screening method, but will definitely improve the screening performance, by selecting the high risk patients for further investigations.

CONCLUSION

In patients with viral hepatitis related cirrhosis, the presence of HCC is associated with increased LS values. Liver cancer may be predicted with good accuracy. This cannot be considered as

an initial screening test in these patients as it has a low sensitivity. It can be used as a confirmatory test to exclude other causes which give rise to high kPa because of high specificity. Liver Stiffness changes, however, seem to be more complex, generating a "shadow" that might be characteristic for HCC, but this finding needs to be further investigated. We believe that such an approach probably could be used to identify patients at high risk or, on the contrary, patients with no risk of HCC in order to decrease the number of useless procedures.

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