

Diagnostic Accuracy of Ultrasound in Detecting Hepatocellular Carcinoma Keeping Histopathology as Gold Standard

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ABSTRACT

Objective: To determine the diagnostic accuracy of USG in detecting hepatocellular carcinoma.

Methodology: This cross sectional validation study was conducted from 0-2-06-2018 till 01-06-2019 at Department of Diagnostic Radiology, Combined military hospital Quetta. A total of 70 patients with liver cirrhosis with mass and age 18-60 years of either gender were included. Nodular lesion <3 cm in size, non-specific vascular profile, poor visualization and FNA / biopsy can cause complications were excluded. All the patients then underwent first ultrasound and then histopathology. The ultrasonography findings were recorded the presence or absence of HCC and correlated with CT scan findings. Mean and standard deviation were calculated for age. Frequency and percentage were calculated for gender

Results: In USG positive patients, 31(44.28%) True Positive had hepatocellular carcinoma and 03(4.28%) False Positive had no hepatocellular carcinoma on histopathology. Among 36 USG negative patients, 04(11.11%) False Negative had hepatocellular carcinoma on histopathology whereas 32 (88.8%) True Negative had no hepatocellular carcinoma on histopathology (p=0.0001). Overall sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of ultrasound in detecting hepatocellular carcinoma keeping histopathology as gold standard was 88.57%, 91.43%, 91.18%, 88.89% and 90.0% respectively.

Conclusion: This study concluded that grey scale ultrasound along with Doppler ultrasound is a simple, non-invasive, economical, readily available imaging modality with high sensitivity and accuracy in diagnosing hepatocellular carcinoma.

Keywords: Accuracy, Hepatocellular carcinoma, Ultrasonography

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Introduction

Liver cirrhosis is the leading cause of Hepatocellular carcinoma (HCC). HCC is third most common cause of death due to cancer and fifth most common cancer as a whole. In developing countries its incidence is 35%. This is two to three times higher than the developed countries.

In Western countries increasing number of cases of HCC are also emerging in patients with non-alcoholic fatty liver disease. It is a highly malignant tumour which shows early metastasis having poor prognosis.¹ Strong and

continuing recent increase in HCC rates have been observed in Western countries where from 15-50% of HCC cases are cryptogenic.²

Most cases of hepatocellular carcinoma (HCC) are associated with cirrhosis secondary to chronic hepatitis B virus (HBV) or hepatitis C virus infection. Most variations in its age, sex and race specific rates among different regions are likely to be related to differences in hepatitis viruses that are most prevalent in a population, the timing of their spread, and the ages of the individuals the viruses infect.³ The

prognosis of HCC is strongly associated to tumor stage having best survival seen in patients diagnosed at early stages. The patient with early-stage HCC can undergo curative treatments and have 5-year survival rates exceeding 70%, there are no curative treatment options for advanced HCC. Survival is typically less than 1 or 2 years, which depends upon the underlying tumor burden, liver function, and performance status.³

The emphasis of the National Institute for Health and Care Excellence (NICE) and The Royal College of Radiologists (RCR) is on early diagnosis as it yields improved prognostic value. They recommend the use of ultrasound (USS) or serum Alpha-fetoprotein (AFP) for the surveillance of clinically suspected mass in patients with chronic liver disease.⁴ As USG is not associated with radiation exposure concerns so it is suitable for the surveillance of HCC as repeated examinations are needed. The use of contrast agents improves the sensitivity and specificity of US; therefore, this method is useful for evaluating the grade of HCC, which is important in determining a treatment plan.⁵ Hepatocellular carcinoma is the most common de novo liver nodule in cirrhosis; the estimated probability that a nodule in cirrhosis is an HCC is more than 80% in nodules ≥ 2 cm in size and between 50 and 75% in nodule less than 2 cm.⁶

A multicenter study of B mode and Doppler ultrasound in focal liver lesions reported frequencies of HCCs, metastasis and intrahepatic cholangiocellular carcinomas (ICCs) in cirrhosis of 76.6, 4.3 and 2.5% respectively. Benign lesions were detected in 14.9% of cirrhosis livers, with 5.7% being large regenerative nodules, 2.8% hemangiomas and 0.3% adenomas.⁸ There is clear evidence from recent studies that CEUS is indeed a useful primary imaging method in the characterization of HCC and diagnostically comparable to CT/MRI for the diagnosis of a typical vascular pattern of HCC in small (2cm) nodules.^{7,8}

Although accuracy of percutaneous needle is around 90% but its use in diagnosis of HCC is controversial due to potential for complications such as bleeding and seeding of tumour cells along the needle track. The sensitivity of ultrasonography for detecting HCC reported in previous studies is 85% and specificity is 94%.⁹

The present study was designed to determine the diagnostic accuracy of CEUS in the diagnosis of HCC

keeping histopathology as gold standard. HCC is not uncommon in our population and early diagnosis and early treatment are of utmost importance to reduce morbidity and mortality. This study will provide us with a technique for diagnosis of HCC in our population and if found to be significantly high, we will share the results of this study to other physicians to formulate future recommendations for it.

Methodology

This cross sectional validation study was done on 70 patients of liver cirrhosis with mass, raised AFP levels and age between 18-60 years of both genders, who were referred by clinician to the Department of Diagnostic Radiology, Combined military hospital Quetta for ultrasonography were selected for the study. The study was conducted from 02-06-2018 till 01-06-2019 after approval from the ethical committee on 01-06-2018. Patients with non-specific vascular profile on USG, in which FNA / biopsy can cause complications and not willing for histopathology were excluded from the study. Sample size of 70 cases has been calculated with 95% confidence level, taking an expected percentage of HCC i.e. 35% and 10% margin of error for the sensitivity of 85% and for the specificity of 94% of Doppler ultrasonography in diagnosing HCC.

After taking informed consent and relevant history, ultrasonography of each patient was done using low frequency curvilinear probe with a frequency of 3.5 MHz. Scanning was done in supine and left lateral position. Images were taken in both radial and anti-radial projections. The position of lesion was described according to the segmental anatomy of liver. All lesions were carefully described sonographically according to their shape, orientation, margins, lesion boundary, interface, echopattern, posterior acoustic features and surrounding tissue alterations. Ultrasonographic guided aspiration from the lesion was done by 18G needle under full aseptic measures. The aspirate was spread on glass-slide and fixed in absolute alcohol. The slides were sent for histopathology. Ultrasonographic findings were validated by histopathology reports. Diagnostic criteria for hepatocellular carcinoma were fine needle aspiration cytology proven cases. To exclude observer bias results were verified by another radiologist. All of the above information including Histopathological reports were recorded.

Collected data was analyzed through computer software SPSS 20.0. Mean and standard deviation were calculated for age. Frequency and percentage were calculated for gender. 2x2 contingency table was used to calculate the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of ultrasonography for diagnosis of hepatocellular taking histopathology as gold standard.

Results

Age range in this study was from 18-60 years with mean age of 44.57 ± 8.07 years. The majority of the patients 41 (58.57%) were between 41 to 60 years of age. Out of these 70 patients, 54 (77.14%) were male and 16 (22.86%) were females with ratio of 3.4:1. (Table I)

Table I: Distribution of patients according to age.

Age (years)	No. of Patients	Age %
18-40	29	41.43
41-60	41	58.57
Total	70	100.0
Mean \pm SD = 44.57 \pm 8.07 years		

All the patients were subjected to first Doppler ultrasonography and then histopathology. USG supported the diagnosis of hepatocellular carcinoma in 34 (48.57%) patients and no HCC in 36 (51.43%) patients. Histopathology findings confirmed hepatocellular carcinoma in 35 (50.0%) cases where as 35 (50.0%) patients' revealed no HCC. In USG positive patients, 31 (44.28%) True Positive had hepatocellular carcinoma and 03 (4.28%) False Positive had no hepatocellular carcinoma

on histopathology. Among 36, USG negative patients, 04 (11.1%) False Negative had hepatocellular carcinoma on histopathology whereas 32 (88.8%) True Negative had no hepatocellular carcinoma on histopathology ($p=0.0001$) as shown in Table II.

Overall sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of ultrasound in detecting hepatocellular carcinoma keeping histopathology as gold standard was 88.57%, 91.43%, 91.18%, 88.89% and 90.0% respectively. (Table III)

Discussion

Imaging modalities for HCC include ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI). Although CT and MRI provide higher-resolution images than ultrasonography, they are also more costly and, in the case of CT, are associated with radiation exposure.^{10,11} Because HCC is typically a hypervascular lesion, CT and MRI are performed with arterial-enhancing contrast agents. Microbubble-enhanced ultrasonography can also be performed, although agents are not yet approved by the U.S. Food and Drug Administration for this purpose, and microbubbles are present in the liver for only a limited duration.¹² Other technical, patient, and tumor factors may also affect test performance.^{13,14} Ultrasound has been used as a non-invasive imaging technique for detection, characterization and staging of various focal lesions. Ultrasonography allows full liver scanning and accurate detection of focal lesions of liver

Table II: Diagnostic accuracy of ultrasound in detecting hepatocellular carcinoma keeping histopathology as gold standard.

	Positive result on Histopathology	Negative result on Histopathology	P-value
Positive result on USG	31 (TP)*	03 (FP)***	0.0001
Negative result on USG	04 (FN)**	32 (TN)****	

*-TP=True positive **-FP=False positive ***-FN=False negative ****-TN=True negative

Sensitivity: 88.57%

Specificity: 91.43%

Positive Predictive Value (PPV): 91.18%

Negative Predictive Value (NPV): 88.89%

Diagnostic Accuracy: 90.0%

Table III: Stratification of age 18-40 years (n=29)

	Positive result on Histopathology	Negative result on Histopathology	P-value
Positive result on USG	14 (TP)	01 (FP)	0.001
Negative result on USG	03 (FN)	11 (TN)	

Sensitivity: 82.35%

Specificity: 91.67%

Positive Predictive Value (PPV): 93.33%

Negative Predictive Value (NPV): 78.57%

Diagnostic Accuracy: 86.21%

parenchyma. Ultrasound examinations are the most frequently used imaging method for evaluation of focal liver lesions.¹⁵

Age range in this study was from 18-60 years with mean age of 44.57 ± 8.07 years. Majority of the patients 41 (58.57%) were between 41 to 60 years of age. Thimmaiah VT et al¹⁶ and Nggada HA et al¹⁷ had found mean age of 41.5 and 47 years respectively.

Demir OI et al¹⁸ in his study found this mean age as 54 years which is a little higher compared to our study. On the other hand, Inan N et al¹⁹ observed mean age of 66 years which is much larger as was observed in our study. In the United States and Europe, the median age at diagnosis is 65 years. Hepatocellular carcinoma is rarely diagnosed in persons younger than 40 years. However, between 1975 and 1998, the 45- to 49-year age group had the highest rate, a 3-fold increase in the incidence of hepatocellular carcinoma. In Africa and Asia, age at diagnosis is substantially younger, occurring in the fourth and fifth decades of life, respectively. Diagnosis at a younger age is thought to reflect the natural history of hepatitis B and C related hepatocellular carcinoma.²⁰ Out of these 70 patients, 54 (77.14%) were male and 16 (22.86%) were females with ratio of 3.4:1. This male predominance was also seen in many previous studies.¹⁶⁻¹⁹ So, our study showed that the majority of patients with liver lesions were presented in 4th and 5th decades of life with male predominance.

All the patients were subjected to first Doppler ultrasonography and then histopathology. USG supported the diagnosis of hepatocellular carcinoma in 34 (48.57%) patients and no HCC in 36 (51.43%) patients. Histopathology findings confirmed hepatocellular carcinoma in 35 (50.0%) cases whereas 35 (50.0%) patients' revealed no HCC. In USG positive patients, 31 (True Positive) had hepatocellular carcinoma and 03 (False Positive) had no hepatocellular carcinoma on histopathology. Among 36, USG negative patients, 04 (False Negative) had hepatocellular carcinoma on histopathology whereas 32 (True Negative) had no hepatocellular carcinoma on histopathology ($p=0.0001$). Overall sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of ultrasound in detecting hepatocellular carcinoma keeping histopathology as

gold standard was 88.57%, 91.43%, 91.18%, 88.89% and 90.0% respectively.

Jouinis S et al²¹ in his study has shown the sensitivity, specificity, positive predictive value and negative predictive value of ultrasonography in diagnosing hepatic lesions was 78.30%, 99.70%, 96.80% and 97.10% respectively. In Sattar S et al study²², mean age of the study population was 60.39 ± 10.9 years. 47 (67.1%) of the patients were males and 23 (32.9%) were females. Risk factors for hepatocellular carcinoma were HCV infection in 27 (38.6%), HBV infection in 11 (15.7%). Mean size of the lesions was 4.59 ± 1.08 cm. The lesions were characterized as being isoechoic, hypoechoic or hyperechoic as compared to the liver parenchyma. Compared to histopathologic findings, the accuracy of the ultrasound findings was determined. Sensitivity of ultrasonography in detection of hepatocellular carcinoma was 92.3%. Specificity was 55.5%. The positive predictive value was 85.7% and negative predictive value was 71.4%.

In a study by Yu, et al²³, which compared the different imaging modalities like US, CT and MRI, the sensitivity of USG in comparison to these varied from 46–85% depending upon the lesion size. It was lowest for the lesion size less than 2 cm which was 46% and with the lesion size greater than 4 cm it was 85%. So sensitivity improved with the increased lesion size while specificity was 96% and 89% positive predictive value.

In a Cross-sectional survey²⁴, conducted in the Department of Diagnostic Radiology, King Edward Medical University/Mayo Hospital, Lahore in one year included a total of 70 patients with focal lesion on ultrasound. After evaluating by Doppler sonography and doing core biopsy, the patients were sent to the department of pathology in Mayo hospital for Histopathological examination. Histopathology was assessed for confirmation of positive and negative cases. Mean age of the patients was 60.9 ± 4.7 years. Out of 70 patients, 47 patients (67.1%) were male while the remaining 23 patients (32.9%) were female. On Doppler sonography 37 cases were positive for hepatocellular carcinoma and 33 cases were negative while 36 cases were positive and 34 negative on histopathology. On Doppler sonography, sensitivity (94.4%), specificity (91.1%), diagnostic accuracy (92.8%), positive predictive value (91.8%)

and negative predictive value was 93.9%.²⁴

In a study by Yu, et al²⁵, which compared the different imaging modalities like US, CT and MRI, the sensitivity of USG in comparison to these varied from 46– 85% depending upon the lesion size. It was lowest for the lesion size less than 2 cm which was 46% and with the lesion size greater than 4 cm it was 85%. So sensitivity improved with the increased lesion size. While specificity was 96% and 89% was positive predictive value. In this study, most of the patients with early HCC diagnosis were included with the help of advanced imaging technology. So many patients were with the smaller lesion size were included which are not readily diagnosed on ultrasonography.

Yasmeen M et al²⁶ in his study found the mean age of patients as 46.98 ± 6.20 years. Mean duration of chronic liver disease was 11.58 ± 3.22 months. Among 246 patients, in 102 (41.5%) patients single lesions were seen, while in 67 (27.2%) patients multiple lesion were seen. Mean size of mass was found to be 4.05 ± 1.37 cm. The diagnostic accuracy of ultrasound for the diagnosis of HCC was 81.71%. The sensitivity and specificity of ultrasound for the diagnosis of HCC was 86.21% and 75.25% respectively. However, in this study positive and negative predictive values for ultrasound were 83.33% and 79.19% respectively.

Conclusion

This study concluded that grey scale ultrasound along with Doppler ultrasound is a simple, non-invasive, economical, readily available imaging modality with high sensitivity and accuracy in diagnosing hepatocellular carcinoma, and has not only dramatically improved our ability of accurate diagnosis of hepatocellular carcinoma but also improved patient care by timely and proper treatment. So, we recommend that Doppler ultrasonography should be used routinely as a prime modality for diagnosing hepatocellular carcinoma.

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