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Role of Fibroscan for early detection of hepatocellular carcinoma (HCC) in hepatitis C cirrhotic patients

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Abstract

Background: Liver cancer (HCC) ranks as the fifth most prevalent cancer worldwide and is ranked third as a common cause of death due to cancer. The benefit of Fibroscan in assessing the risk of developing liver cancer that was evaluated in this work was not fully demonstrated. The aim of this work was to study the role and clinical significance of Fibroscan for early detection of liver cancer in hepatitis C patients with cirrhosis.

Results: As regards binary logistic regression for predictors of HCC, it was found that Child C, AST, Fibroscan, and AFP were predictors for developing HCC. Liver stiffness values were significantly high in all groups, and the specific cutoff value for hepatocellular carcinoma detection was above 24 kPa in hepatitis C virus patients. Therefore, liver stiffness of more than 24 kPa can be considered as an independent risk factor for the development of liver cancer in HCV patients.

Conclusion: Liver stiffness of more than 24 kPa was an independent risk factor for developing new liver cancer in HCV patients.

Keywords: HCC, Fibroscan, Liver disease, Cirrhosis, Prediction, Prevalence

Background

Liver cancer (HCC) ranks as the fifth most prevalent cancer worldwide, and is ranked third as a common cause of death due to cancer [1, 2]. In Egypt, the prevalence of hepatocellular carcinoma increased markedly in the last decade due to the high prevalence of hepatitis C virus and the improved survival for cirrhotic patients allowing time for some of them to develop HCC [3–8].

For improvement in the fate of liver cancer, adequate treatment after early detection is important. To this end, it is critical to identify high-risk groups for liver cancer and to conduct appropriate screening in the clinical practice of chronic liver disease [9, 10].

It has been postulated that hepatitis virus infection, old age, male sex, liver cirrhosis alanine aminotransferase (ALT) elevation, low albumin (Alb), low platelets (Plt), and α-fetoprotein (AFP) elevation are risk factors for HCC; however, liver cirrhosis is the most important risk factor irrespective of its etiology [11, 12].

Liver cirrhosis has been evaluated by liver biopsy, as the histology is the gold standard for quantitative fibrosis assessment; but liver biopsy is associated with several problems such as invasiveness, sampling errors, and diagnostic differences between pathologists. This makes it unpopular among patients and impractical for serial assessments of patients with chronic liver disease. With the development of Fibroscan using transient elastography, it became possible to estimate the elasticity of the liver [13, 14]. An accurate quantification of the degree of liver fibrosis is necessary for prognosis and guiding surveillance [15].

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The accuracy of Fibroscan diagnosis of cirrhosis has been widely recognized in many chronic liver diseases except for some liver conditions such as congestion, severe infections, or cholestasis, which may be overestimating cirrhosis with Fibroscan [16].

Recently, the risk of liver cancer was assessed based on liver stiffness measured by Fibroscan among the European population [17]; however, in most reports, the risk of liver cancer has been indirectly assessed based on the value of cirrhosis as measured by Fibroscan; however, HCC-associated liver stiffness was not directly assessed [18].

Additionally, the effectiveness of Fibroscan in predicting the risk of HCC has not been fully elucidated that is assessed in this work. The aim of this work was to study the role and clinical significance of Fibroscan for early detection of HCC in hepatitis C cirrhotic patients.

Methods

This was a cross-sectional study included fifty (50) HCV patients with liver cirrhosis selected from a major university hospital. Approval of the study was obtained by the institutional ethical committee. They were divided into two groups as the following: group I: included 25 HCV cirrhotic patients with HCC and group II: included 25 HCV cirrhotic patients without HCC.

Inclusion criteria: adult HCV cirrhotic patients above 18 years, with or without hepatocellular carcinoma (HCC)

Exclusion criteria: hepatic encephalopathy, ascites or pregnancy, hepatorenal syndrome or hepato-pulmonary syndrome, right side heart failure (liver congestion), extra hepatic tumors, history of liver transplantation, cholestasis, and hepatitis B patients

An informed written consent was obtained for each involved patients for approval to participate in this study. All patients were subjected to the following: full history taking and clinical examination including information on age, sex, gastrointestinal symptoms, comorbidities (diabetes mellitus (DM), hypertension (HTN), and congestive heart failure (CHF)), hepatic encephalopathy, renal impairment, liver transplantation, tumors, and medications.

Blood samples were collected from the patients by vacuum venipuncture, using a dry sterile 5-ml tube. The serum was separated, centrifuged, and aliquoted. Laboratory investigations were done for all the patients including the following: liver function tests as liver enzymes (ALT-AST), serum albumin, bilirubin, prothrombin time and INR, viral hepatitis markers (HBs Ag, anti-HBc, and anti-HCV), complete blood picture and erythrocyte sedimentation rate (ESR), kidney function tests (blood urea and serum creatinine), and serum α-fetoprotein (AFP).

Imaging was performed for all the patients including the following: (a) abdominal ultrasonography, reporting data for liver echogencity, vascularity (portal and hepatic veins), intrahepatic biliary dilation, and focal lesion criteria (site, number, size, and echogencity); also report about the spleen, kidneys, lymph nodes, ascites, and any other abnormality if present. (b) Contrast-enhanced triphasic computerized tomography (CT) confirming HCC diagnosis. (c) Fibroscan on the liver: liver stiffness measurement (LSM) using Fibroscan 402 (Echosens, Paris, France) was done.

Principle of technique: it measures liver stiffness as it is a rapid technique taking less than 5 min that can be easily performed at bedside or in outpatient clinic. It is a noninvasive and painless technique, with results immediately available and it can be safely repeated for follow-up. The results are expressed in kilopascals (kPa), corresponding to the median value of 10 validated measurements according to the manufacturer's recommendations and the machine scale result ranges from 2.5 to 75 kPa with normal value around 5.5 kPa. The validity results also depend on two important parameters: the interquartile range, which reflects the variability of the validated measures and should not exceed 30% of the median value; the success rate (the ratio of the number of successful measurements to the total number of acquisitions) should be at least 60%.

Technique: the patient was instructed to lie supine. An ultrasound-like probe was placed on the skin over the liver area, typical in the right mid axillary line. The patient felt a gentle flick each time a vibration wave is generated by the probe. Then the patients were evaluated practically according to the following scores:

Modified Child score: evaluation of the severity of liver cirrhosis was obtained in each cirrhotic patient with modified Child-Pugh score. This system relies on clinical and laboratory evaluation including ascites, grade of encephalopathy, serum albumin, bilirubin, and prothrombin time.

Model of End-stage Liver Disease (MELD) score: this is a model for end-stage liver disease for evaluation of the severity of liver cirrhosis in each cirrhotic patient, and this system relies on laboratory evaluation including serum bilirubin, serum creatinine, and INR (international normalized ratio). MELD score = $9.6 \times \log$ (creatinine mg/dl) + $3.8 \times \log$ (bilirubin mg/dl) + $11.2 \times \log$ (INR) + 6.4.

Statistical analysis: statistical presentation and analysis of the present study was conducted, using the mean, standard deviation, and chi-square test by SPSS V.16. Chi-square test was used for comparison between two groups as regards qualitative data. Significance level (P) value was expressed as follows: P value ≥ 0.05 was considered statistically non-significant; P value < 0.05 was considered statistically significant; P value < 0.001 was considered statistically highly significant.

Results

This study included fifty HCV cirrhotic patients who were divided into two groups: group I, included 25 HCV cirrhotic patients (16 male and 9 female) with hepatocellular carcinoma and group II, included 25 HCV cirrhotic patients (12 male and 13 female) without evidence of hepatocellular carcinoma. Age and sex were cross matched between the two studied groups. The demographic data of both groups are shown in Table 1.

As regards the reported clinical data, 13 patients (52%) in group I and 3 patients (12%) in group II presented by jaundice, while 20 patients (80%) in group I and 9 patients (36%) in group II presented by clubbing. Nineteen patients (76%) in group I and 10 patients (40%) in group II presented by ecchymosis, and hepatomegaly was detected in 2 patients (8%) in group I and 6 patients (24%) in group II; feeling of hard liver was detected in 10 HCC patients (40%) compared to HCV cirrhotic patients without HCC with a significant statistical difference. Splenomegaly was detected in 18 patients (72%) in group I and 20 patients(80%) in group II, while 15 patients (60%) in group I and 10 patients (40%) in group II suffered from abdominal pain; while 20 patients (80%) in group I and 16 patients (64%) in group II suffered from easy fatigability, 22 patients (88%) in group I and 20 patients (80%) in group II suffered from loss of weight. Jaundice, clubbing, and ecchymosis were more in HCC patients than in cirrhotic patients with a significant statistical difference. No patients had ascites or hepatic encephalopathy. Comparison between both groups according to clinical data is shown in Table 2.

Table 1 Comparison between the two studied groups according to their demographic data

	Group I (*n* = 25)		Group II (*n* = 25)		*P*
	No.	%	No.	%	
Sex					
Male	16	64.0	12	48.0	0.254
Female	9	36.0	13	52.0	
Age (years)					
Min.–Max.	40.0–62.0		37.0–50.0		0.918
Mean ± SD	56.36 ± 4.83		46.20 ± 6.01		
Median	50.0		45.0		
Occupation					
Farmer	14	56.0	11	44.0	0.396
Non-farmer	11	44.0	14	56.0	
BMI (kg/m²)					
Min.–Max.	22.0–26.0		20.98–25.23		0.018*
Mean ± SD	24.49 ± 1.0		23.66 ± 1.39		
Median	24.60		24.11		

Comparison between the two studied groups according to median and IQR of Fibroscan is shown in Table 3.

As regards binary logistic regression for predictors of HCC, it was found that Child C, AST, Fibroscan, and AFP were predictors for developing HCC. The highest odds ratio was Child C (*P* 0.035) followed by AFP (*P* 0.058) then Fibroscan (*P* 0.88) and AST (*P* 0.76). This is well demonstrated in Table 4.

As regards AFP values, values were higher in HCC patients than in cirrhotic patients (*P* = 0.003), with a significant difference between the studied groups. Liver stiffness values were significantly high in all groups, and the specific cutoff value for hepatocellular carcinoma detection was above 24 kPa in hepatitis C virus patients. Therefore, liver stiffness of more than 24 kPa can be considered as an independent risk factor for the development of liver cancer in HCV patients. The cutoff values for Fibroscan and AFP as markers for HCC are shown in Table 5.

Discussion

The presence of cirrhosis represents a key risk factor for the development of HCC. The HCC incidence rate of cirrhosis is 2–4% per year, so patients with cirrhosis constitute a high risk group for effort at prevention and early detection [19].

So in this study, we aimed to determined role and clinical significance of Fibroscan for early detection of HCC in hepatitis C Cirrhotic patients. In order to achieve this goal, we selected fifty subjects who were divided into two groups: group I included 25 HCV cirrhotic patients (16 male and 9 female) with hepatocellular carcinoma, while group II included 25 HCV cirrhotic patients (12 male and 13 female) without evidence of HCC.

In the current study, AFP in cases of liver cancer (HCC) had an average value of 317.5 ng/ml which was statistically higher than patients with cirrhosis (10.8 ng/ml). These results are consistent with Jiang et al. [20] who reported that AFP in cases of liver cancer had an average value of 384.6 ng/ml which was statistically higher than patients with cirrhosis (26.04 ng/ml).

On the other hand, other studies have shown that the role of AFP in diagnosing liver cancer is limited, and these results were supported by El-Serag et al. [21] who stated that AFP was not elevated in all patients with liver cancer. Its sensitivity to detect liver cancer is 79%; the specificity is also 89% and not 100% because AFP in the serum can also be detected in patients with cirrhosis and chronic hepatitis. This was supported by Abdel-Rahman et al. [22] who stated that the AFP level is always normal in patients with small HCC and does not rise significantly in patients with early stage, and curable liver cancer may be offset. Huaibin et al. [23] also concluded that

Table 2 Comparison between the studied groups according to clinical data

Clinical data	Group (I) HCC **n** = 25		Group (II) cirrhosis **n** = 25		**P** value
	n	%	**n**	%	
Jaundice	13	52	3	12	0.03*****
Clubbing	20	80	9	36	< 0.001*****
Ecchymosis	19	76	10	40	0.02*
Hepatomegaly	2	8	6	24	0.5
Hard liver	10	40	0	0	0.004*
Splenomegaly	18	72	20	80	0.13
Abdominal pain	15	60	10	40	0.903
Easy fatigability	20	80	16	64	0.65
Loss of weight	22	88	20	80	0.865

*Significant

the AFP level in the blood was a poor diagnostic indicator in liver cancer patients.

In our study, the ROC analysis of AFP when used as a diagnostic test indicates that a value of around 26.15 ng/ml provides the optimum balance between sensitivity and specificity, but at this level the sensitivity is only 79% and specificity is 89.5%. This is consistent with Jiang et al. [20] who reported that the sensitivity of AFP was around 79.7% and with specificity of about 80.3% in cases of liver cancer.

So as a need of new screening tools, this work studied Fibroscan as a noninvasive method for measuring liver stiffness as a risk and diagnostic predictors for HCC.

Our data reported that TE may be a useful and promising noninvasive method for liver fibrosis assessment and it is a good diagnostic predictor for HCC development in HCV cirrhotic patients.

The present study reported cutoff value of 24 kPa for diagnostic prediction of HCC with sensitivity 100%, specificity 83.3%, PPV 94.5%, NPV 77.3%, and AUC 89%.

Singh et al. [24] reported that the degree of liver stiffness was associated with risk of decompensated cirrhosis, HCC,

and death in patients with CLDs. LSM therefore might be used in risk stratification.

Tatsumi et al. [2] reported liver stiffness measurement in their work for risk assessment of hepatocellular carcinoma and found that in HCV, liver stiffness of more than 12.0 kPa was an independent risk factor for new HCC development. Collectively, determining the fibrotic cutoff values for HCC concurrence would be important in evaluating HCC risks.

Staging hepatitis C in seven categories using transient elastography (Fibroscan) was determined by Poynard et al. [25] who suggested that TE increase was associated with the occurrence of all severe complications including hepatocellular carcinoma, hepatic insufficiency.

Also, in the study of Adler et al. [17] which was a retrospective observational study shows an association between liver stiffness measurements at the upper extreme and increasing HCC risk in patients with cirrhosis. LSM by Fibroscan allows stratification of HCC risk in a noninvasive and reliable way [26–30].

The limitation of the study was that it was centered at the hepatitis C cirrhosis patients. We will consider application of this idea in hepatitis B cirrhosis and other etiologies of chronic liver disease in future research.

Table 3 Comparison between the two studied groups according to median and IQR of Fibroscan

	Group I (**n** = 25)	Group II (**n** = 25)	**T**	**P**
Median of Fibroscan				
Min.–Max.	18.0–68.5	14.0–36.0	18.086*	< 0.003*
Mean ± SD	42.08 ± 6.92	25.2 ± 3.0		
Median	40.0	24		
IQR of Fibroscan				
Min.–Max.	4.0–16.0	1.80–11.60	16.723*	< 0.003*
Mean ± SD	9.08 ± 0.81	5.21 ± 0.27		
Median	8.0	4.8		

Table 4 Binary logistic regression for significant risk factors or predictors of HCC

Parameter	**X** regression	**P**	Odds ratio	Lower	Upper
Child C	3.08	0.035	7.08	1.02	68.62
AST	0.003	0.765	0.65	0.876	1.09
Fibroscan	0.001	0.88	0.76	0.73	1.01
AFP	2.22	0.058	0.83	0.76	1.05

Table 5 Fibroscan and AFP cutoff values as markers for HCC

Test	Cutoff	Sensitivity %	Specificity %	PPV %	NPV %	AUC %	*P* value
Fibroscan (kPa)	24	98.2	83.8	94.5	77.3	89	**0.000***
AFP (ng/ml)	26.15	79	89.5	97.5	96.3	83.2	**0.001***

*Significant

Conclusion

Fibroscan can be a good technique for detection of HCC high-risk cirrhotic patients and can be of great added value if incorporated in the current HCC screening protocols in hepatitis C cirrhotic patients. Our work is unique in selecting the studied patients of the same etiology (HCV) aiming an accurate results for this category of patient that represent the majority of HCC in Egyptian patients, while previous studies evaluated patients of different etiologies and each etiology has its own calibration on Fibroscan machine.

Abbreviations
AFP: Alfa-fetoprotein; Alb: Albumin; ALT: Alanine transaminase; AST: Aspartate transaminase; BMI: Body mass index; CBC: Complete blood count; DM: Diabetes mellitus; Hb: Hemoglobin; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; HTN: Hypertension; IQR: Interquartile range; LSM: Liver stiffness measurement; No: Number; PCR: Polymerase chain reaction; PLT: Platelets; ROC: Receiving operator curve; SD: Standard deviation; SVR: Sustained virological response; USA: United States of America; WBCs: White blood cells

Authors' contributions
AE, MS, and SA were responsible for the concept, design, definition of intellectual content, and manuscript preparation. AE, MS, SA, and SA-E were responsible for literature search, manuscript review, and manuscript editing. AE, MS, MH, MY, SA, and SA-E were responsible for data acquisition and clinical studies. MH and SA-E were responsible for data analysis and statistical analysis. All authors have been read and approved the final version of the manuscript.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The research was approved from Tanta University, Faculty of Medicine Research ethical committee. The approval number is 30679/04/16. An informed written consent was taken from each patient. The study protocol complies with the ethical guidelines of the 1975 Declaration of Helsinki as reflected in prior approval by the institution's Human Research Committee.

Consent for publication
All patients included in this research gave written informed consent to publish the data contained within this study. If the patient was less than 16 years old, deceased, or unconscious when consent for publication was requested, written informed consent for the publication of this data was given by their parent or legal guardian.

Competing interests
The authors declare that there is no conflict of interest.

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