Role of Transient Elastography (Fibroscan) in Early prediction of Hepatitis C Virus Related Hepatocellular Carcinoma

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ORIGINAL ARTICLE

Role of Transient Elastography (FibroScan) in Early Prediction of Hepatitis C Virus-related Hepatocellular Carcinoma

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Abstract

Background: Hepatocellular carcinoma (HCC) is the fifth-leading cause of cancer-related deaths globally. Liver biopsy is the gold standard for diagnosing liver fibrosis and cirrhosis. Instead of a liver biopsy, there are many noninvasive diagnostic tools for assessing hepatic fibrosis as a risk factor for HCC, such as FibroScan.

Aim of the study: Assess the role of transient elastography (FibroScan) in the prediction of (HCC) in chronic hepatitis C virus patients.

Patients and methods: A case−control study that included 133 patients with cirrhosis and HCC and 133 patients with HCV-liver cirrhosis without HCC was carried out. Each patient had their medical history and thorough clinical examination done. They were assessed for liver stiffness using FibroScan. All patients underwent triphasic CT scan, and routine laboratory investigations were taken from each patient such as liver function test, CBC, and tumor markers.

Results: Males resembled the majority, and patients with HCC were significantly older than those without HCC (P value < 0.001). Our data shows that sensitivity analysis of liver stiffness measured by transient elastography (FibroScan) can be used to discriminate between the cirrhotic group without HCC and HCC group at a cutoff level of>24.3, with 90.5% sensitivity, 85.7% specificity, 86.4% PPV, and 90% NPV (AUC = 0.941 and P-value less than 0.001).

Conclusion: FibroScan can significantly predict HCC among patients post-HCV treatment using a cutoff point of liver stiffness>24.3 kPa.

Keywords: Cirrhosis, FibroScan, Hepatocellular carcinoma, Liver stiffness

1. Introduction

Liver cell carcinoma (HCC) is the fifth most commonly diagnosed malignancy globally and the third main factor for cancer-related mortality.[1,2] Because of the prominent incidence of the hepatitis C virus and enhanced survival for cirrhotic patients, the prevalence of hepatocellular carcinoma in Egypt has grown significantly throughout the previous decade.[3−5]

Improved liver cancer prognosis requires early detection and effective therapy. To that purpose, it is essential to define the high-risk populations for liver cancer and implement adequate screening and early detection programs for patients diagnosed with chronic liver disease.[6,7]

It has been proposed that hepatitis virus infection is the primary cause of HCC and is correlated to poor prognosis due to poor liver function of the underlying cirrhotic liver[8]; nevertheless, hepatic

cirrhosis is the significant risk factor irrespective of its origin.[9]

Obtaining a histopathological diagnosis is the standard of care for the quantitative evaluation of liver fibrosis. Unfortunately, liver biopsy has many drawbacks such as invasiveness, sampling errors, and interobserver variability, because of these features liver biopsy is unfeasible for serial examinations of chronic liver disease patients and follow-up.[10]

Recently, many noninvasive diagnostic tools have been proposed for early diagnosis of primary liver tumors and follow-up of cirrhotic patients. Fibro-Scan became feasible to assess the elasticity of liver by employing transient elastography.[11] The severity of liver fibrosis must be accurately determined for patient prognosis and monitoring.[12]

Recently, a study has correlated liver stiffness measured by FibroScan with risk for the development of HCC in the European population[13]; however, the risk of HCC was extrapolated from the degree of cirrhosis measured by FibroScan indicating that HCC-related liver stiffness could not be precisely evaluated.[14]

Thus, our goal was to assess the role of transient elastography (FibroScan) in the prediction of HCC in chronic hepatitis C virus patients.

2. Patients and methods

We conducted a case–control study including 133 HCC patients. They were recruited from the multidisciplinary HCC Clinic at Kasr-Ainy Hospital, Cairo University, Egypt, and Cairo University's Endemic Medicine Department. We recruited 133 patients with liver cirrhosis without HCC to serve as a control group. Before enrollment in the study, all participants gave their informed consent in the period from February 2022 to August 2022. All patients with chronic HCV infection or hepatitis C-related HCC, who did not receive any previous treatment for HCC, were eligible for inclusion in the current study.

HCC was diagnosed based on American Association for the Study of Liver Diseases (AASLD) guidelines, using computerized tomography (CT) or magnetic resonance imaging (MRI) techniques and alpha-fetoprotein (AFP).[15] Patients with chronic liver diseases other than HCV, example, HBV, alcohol-related, autoimmune liver disease and patients coinfected with HIV and HCC patients who receive any previous treatment to HCC, were excluded from the final analysis.

All studied patients were subjected to the following: personal history (such as name, age, gender, occupation, residence, and special habits of

medical importance) and past medical history (DM, HCV, HBV infection, HCC, and blood transfusion). Clinical assessment which includes general examination: For evidence of stigmata of chronic liver disease (jaundice, fetor hepaticus, impaired consciousness, palmer erythema, spider naevi, finger clubbing, jaundice, gynecomastia, feminine distribution of pubic hair, testicular atrophy, cachexia, and peripheral edema). Abdominal examination: with special emphasis on the liver: size, border, surface, consistency, tenderness, pulsation and the spleen: size, notch, and ascites and dilated veins.

Baseline laboratory tests including complete blood count (CBC), liver function tests, ALT and AST, albumin, INR and total/direct bilirubin, renal functions (urea, creatinine), and alpha-fetoprotein (AFP) were assessed using the latex immunoturbidimetric method, and viral hepatitis markers including HCV Ab and HBVs Ag using the ELISA technique.

Pelviabdominal ultrasound was done by the same operator for all patients for examination of liver echotexture and size, size of spleen, presence or absence of ascites, tumor characteristics (focal lesion site, size and number, portal vein, and abdominal lymph node assessment). Triphasic CT of the abdomen and pelvis was done to diagnose and for the staging of HCC.

Transient Elastography (FibroScan): Patients were placed in the dorsal decubitus posture with the right arm at the maximum abduction, and the probe was applied to the right hepatic lobe through intercostal spaces. The probe's transducer tip was placed between the ribs and coated with a coupling gel. The operator detected a portion of the liver free of large vascular structures and distant from HCC with the help of ultrasonic time-motion imaging. Each patient underwent up to 10 successful measurements. The success rate of at least 60% was reliable. If the interquartile range (IQR) to median value ratio was less than 0.30, only then is the median value of successful measurements chosen as representative of the LSM value in a given patient.[16] The following criteria were used to diagnose cirrhosis: transient elastography values greater than 14 kPa, histology, and radiographic or endoscopic indications of portal hypertension.[17]

2.1. Sample size

We used a convenient period sampling, which included all eligible patients who were assessed in the multidisciplinary HCC clinic at Kasr-Ainy Hospital from Feb 2022 to Aug 2022.

2.2. Ethical considerations

The study protocol was reviewed and approved by the ethics committee of Al-Azhar University (Ethical approval number, 000089).

2.3. Statistical analysis

The Statistical Package for the Social Sciences (SPSS), version 28 was used to code and enter the data (IBM Corp., Armonk, NY, USA). Quantitative data were summarized using mean, standard deviation, median, minimum, and maximum; categorical data were described using frequency (count) and relative frequency (%). Nonparametric Kruskal−Wallis and Mann−Whitney tests were used to compare quantitative variables. To compare categorical data, the Chi-square (2) test was used. When the anticipated frequency is < 5, the exact test was used in its place. The Spearman correlation coefficient was used to determine correlations between quantitative variables. P-values greater than 0.05 were regarded as statistically significant.

3. Results

A case−control study included 133 patients with liver cirrhosis and 133 patients with HCC was conducted. Tables 1−6.

In the current study, most of the HCC lesions were solitary accounting for 55.6%, followed by > 3 lesions in 24.8%, then two lesions in 15.8%, and three lesions in 3.8%, with a mean size of all lesions being 4.25 ± 2.45 cm.

Using the ROC curve, it was shown that FibroScan can be used to predict HCC using a cutoff level of

Table 1. *Basic characteristics of the studied groups. Patients with HCC were significantly older and the majority of them were males (P value < 0.001).*

	Liver cirrhosis group ($n = 133$)		HCC group ($n = 133$)		P value
Sex					
Male	49	36.8%	105	78.9%	<0.001
Female	84	63.2%	28	21.1%	
Age (years)					
Median (IQR)	54.0 (37.0−57.0)		63.0 (56.0−68.0)		<0.001
Range	19.0−73.0		34.0−75.0		
BMI (kg/m2)					
Median (IQR)	23.80 (21.74−28.70)	24.40 (22.10−28.30)			0.329
Range	19.50−34.0	19.5−30.10			

The studied groups did not differconcerning their weight, height, or BMI.

Table 2. *Comparisons between the studied groups as regards medical history. Patients with HCC were far more likely to smoke cigarettes (P value 0.003).*

	Groups				P value
	Liver cirrhosis group		HCC group		
Diabetes mellitus	3	2.3%	5	3.8%	0.473
Cigarette smoking					
Nonsmoker	109	82.0%	88	66.2%	0.003
X-smoker	0	0.0%	6	4.5%	
Smoker	24	18.0%	39	29.3%	
Smoking duration (years)					
Median (IQR)	21.50 (18.5−30.0)		22.0 (20.0−40.0)		0.257
Range	3.0−40.0		5.0−50.0		
Blood transfusion	6	4.5%	14	10.5%	0.063
History of hematemesis and melena	21	18.75%	32	24.06%	0.091
History of hepatic encephalopathy	17	12.78%	29	21.80%	0.052
Treated with Sof/Dacla 12 wk	88	66.17%	73	54.89%	
Treated with Sof/Dacla 24 wk	5	3.76%	7	5.26%	
Treated with Sof/Dacla/Riba 12 wk	38	28.57%	46	34.59%	
Treated with Sof/Dacla/Riba 24 wk	0	0.00%	1	0.75%	
Treated with Sof/Led 12 wk	1	0.75%	0	0.00%	
Treated with Sof/Led/Riba 12 wk	0	0.00%	3	2.26%	
Treated with Sof/Led/Riba 24 wk	0	0.00%	1	0.75%	
Treated with INF/Sof/Riba 12 wk	1	0.75%	2	1.50%	

In addition, we found no significant difference among the studied groups regarding diabetes mellitus or previous blood transfusion, history of hematemesis and melena, as well as history of hepatic encephalopathy (P-value>0.05).

Table 3. Comparisons between the studied groups as regards abdominal examination. There were highly statistically significant differences between studied groups as regards liver and spleen size (P-value<0.001); the groups did not differ regarding the presence of ascites (P-value>0.05).

	Groups				P value
	Liver cirrhosis group ($n = 133$)		HCC group ($n = 133$)		
Liver size					
Average	127	95.5%	96	72.2%	<0.001
Enlarged	6	4.5%	16	12.1%	
Shrunken	0	0.0%	21	15.8%	
Spleen					
Average	125	94.0%	58	43.6%	<0.001
Enlarged	7	5.3%	74	55.6%	
Surgically removed	1	0.8%	1	0.8%	
Ascites	0	0.0%	4	3.0%	0.122

Table 4. Radiological characteristics of hepatic lesions among the HCC group.

Triphasic CT results	Number (percent)
Number of lesions	
1 lesion	74 (55.6%)
2 lesions	21 (15.8%)
3 lesions	5 (3.8%)
>3 lesions	33 (24.8%)
Size of lesions in cm	
Mean ± SD	4.25 ± 2.45

Table 6. Comparisons between the studied groups as regard steatosis grade, CAP, and liver stiffness measurements.

	Groups				P value
	Liver cirrhosis group ($n = 133$)		HCC group ($n = 133$)		
Steatosis grade					
S0	69	51.9%	92	69.2%	0.001
S1	19	14.3%	22	16.5%	
S2	27	20.3%	8	6.0%	
S3	18	13.5%	11	8.3%	
CAP					
Median (IQR)	224.0 (201.0−267.0)		201.0 (176.0−243.0)		<0.001
Range	100.0−400.0		100.0−346.0		
Liver stiffness					
Median (IQR)	23.50 (18.5−30.0)		26.0 (20.0−40.0)		<0.001
Range	3.0−40.0		5.0−50.0		

Our study showed that patients with HCC had significantly lower steatosis as measured by CAP using transient elastography (P-value<0.001). Regarding steatosis score; 85.7% of patients with HCC had no or mild steatosis (S0 and S1) as compared with 66.2% of patients without HCC. On the opposite side, patients with HCC had significantly higher liver stiffness as compared with patients without HCC (P-value<0.001).

Liver biopsy is the gold standard that can be used to diagnose liver fibrosis and cirrhosis, although it is an invasive technique with rare but potential consequences. Instead of a liver biopsy, a number of noninvasive indicators for assessing hepatic fibrosis as a risk factor for HCC have been proposed.[20,21]

Except for hepatic congestion, severe hepatic infections, or cholestasis, which may overestimate cirrhosis with FibroScan, the accuracy of Fibroscan diagnosis of hepatic cirrhosis has been largely proven in many chronic liver diseases.[22]

Recently, liver cancer risk in the European population was examined using FibroScan measurements of liver stiffness.[13] Furthermore, the efficiency of FibroScan in determining the probability of HCC has not been fully investigated.[10]

Thus, we carried out a case−control research to assess the role of transient elastography (FibroScan)

>24.3, with 90.5% sensitivity, 85.7% specificity, 86.4% PPV, and 90% NPV (AUC = 0.941 and P value < 0.001) (Table 7, Fig. 1).

4. Discussion

Hepatocellular carcinoma (HCC) is the fifth most cause of cancer-related death worldwide.[18] Although there has been substantial progress in attaining a high sustained virological response (SVR) in individuals with liver cirrhosis, the risk of developing HCC remains roughly 1% per year after reaching SVR.[19]

Table 5. Laboratory characteristics of the studied groups.

	Liver cirrhosis group			HCC group			Mann−Whitney U test	
	Median	Min.	Max.	Median	Min.	Max.	Test value	P value
Hemoglobin	13.0	8.5	17.7	11.9	1.0	18.4	2.320	0.02
WBC	5.6	2.3	12.7	5.9	2.2	57.0	0.678	0.498
Platelets	224.0	40.0	440.0	129.50	36.0	336.0	8.348	<0.001
Total bilirubin (mg/dl)	0.69	0.10	7.00	1.20	0.10	7.00	−8.152	<0.001
AST (U/L)	47.00	7.00	565.00	73.00	7.00	565.00	−6.936	<0.001
ALT (U/L)	47.00	4.30	551.00	66.00	4.30	551.0	−3.737	<0.001
Albumin (g/dl)	4.1	2.00	4.60	3.73	2.00	4.60	−9.840	<0.001
INR	1.00	0.90	1.67	1.3	1.00	2.11	−8.730	<0.001
AFP (ng/mL)	3.5	0.50	77.28	62.5	2.3	61344.0	−10.96	<0.001

Patients with HCC had significantly lower hemoglobin level and platelet count and higher white blood cell count as compared with patients with liver cirrhosis without HCC. In addition, patients with HCC showed significantly more deteriorated synthetic liver functions (higher bilirubin and lower serum albumin and INR); they also had higher liver enzymes and serum AFP (P value < 0.001).

Table 7. Diagnostic performance of FibroScan in the discrimination of liver cirrhosis and HCC in chronic HCV patients.

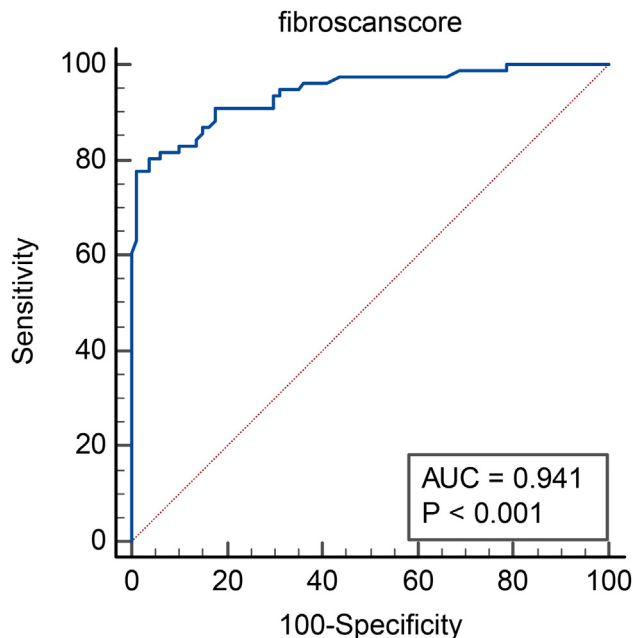|	Cut off	AUC	Sensitivity	Specificity	PPV	NPV	P value
FibroScan	>24.3	0.941	90.5%	85.7%	86.4%	90%	<0.001

Fig. 1. ROC curve of FibroScan in the discrimination of liver cirrhosis cirrhotic group and HCC group.

in the early detection of HCC in chronic hepatitis C virus patients. The study was conducted on 133 patients with liver cirrhosis but no HCC and 133 patients with cirrhosis and HCC.

Our results showed that the HCC group was significantly older and with male predominance (P-value<0.001). Cigarette smoking was significantly more common in patients with HCC (P-value 0.003).

These results were in accordance with many reports in the literature that revealed that old age, male gender, and cigarette smoking were correlated with a higher risk for the development of HCC. HCC incidence peaks at the age of 70 years, while cases before the age of 40 years are extremely rare.[23] As well, between 250,000 and 1,000,000 new cases are reported globally each year with a male predominance and male-to-female ratio of 2:1 and in some countries 4:1.[24] Some reports showed that males not only have higher incidence but also a higher relapse rate.[25]

However, the findings in our study were inconsistent with the study by Ebrahim et al.,[10] who conducted a case−control study including 25 cirrhotic patients and 25 HCC patients and results showed that the HCC group had significantly higher BMI, while age and gender were not significantly

different. Reasons for this include the small sample size of the later research compared with the current one.

Regarding liver and spleen size, there was a remarkable statistically significant difference between the analyzed groups in the current study (P-value<0.001). Our results are consistent with a large cohort study that stated that having a larger spleen capacity is a major predictor of developing HCC (HR = 2.13, P = 0.009).[26]

Shrunken liver is a common finding in the late stages of liver cirrhosis, which is well known as the most prevalent underlying etiology of HCC development on top of cirrhosis as HBV- and HCV-induced liver cirrhosis increase the risk of HCC up to 8.73-fold and 7.07-fold, respectively.[27]

These findings disagree with the study by Ebrahim et al.,[10] who stated that the prevalence of hepatomegaly and splenomegaly was similar between study groups with P values > 0.05, which can be explained by the limited sample in the later study.

Within this research, patients with HCC had significantly lower hemoglobin level and platelet count and higher white blood cell count as compared with patients with cirrhosis of the liver but no HCC. In addition, patients with HCC demonstrated noticeably worsened synthetic liver functioning (higher bilirubin and lower serum albumin and INR); they also had higher liver enzymes and serum AFP (P value < 0.001).

These findings are consistent with many reports in the literature stating that erythropoietin and thrombopoietin are produced by the liver and kidneys. It stimulates the production and differentiation of megakaryocytes into mature platelets. During liver cirrhosis and HCC advancement, a marked decline of those factors has been reported leading to anemia and low platelet count.[28−30]

Alpha-feto protein, a diagnostic test for HCC among cirrhotic patients with a cutoff point of 400−500 ng/mL, is regarded as diagnostic for HCC reaching a specificity of 100%[31]; other studies reported lower cutoff points as 20 ng/mL as the cutoff point, the sensitivity rose to 78.9%, although the specificity declined to 78.1%.[32]

In this study, total bilirubin and INR are one of the components for Child−Pugh and BCLC classifications; elevated total bilirubin and/or bilirubin indicates advanced stages of HCC, which can explain the higher level of INR and low albumin[33,34].

Regarding steatosis, the current study showed that HCC patients had significantly lower steatosis as measured by CAP using transient elastography (P value < 0.001). Regarding steatosis score, 87.7% of patients with HCC had no or mild steatosis (S0 and S1) as compared with 66.1% of patients without HCC. On the opposite side, patients who had HCC had also significantly higher liver stiffness in comparison to patients without HCC (P value < 0.001).

In patients with chronic HCV, hepatic steatosis has been associated with a greater risk of HCC, coupled with obesity and diabetes mellitus. With a prevalence ranging from 31% to 72%, hepatic steatosis is a well-established histopathologic characteristic of chronic HCV.[35]

Ohata et al.[36] demonstrated that hepatic steatosis elevated the likelihood of developing HCC in patients with chronic HCV. When compared with those with no steatosis, those with steatosis had a 2.81 times higher likelihood of getting HCC.

A sedentary lifestyle and imbalanced dietary calories lay the foundation for nonalcoholic fatty liver (NAFL), which can evolve into nonalcoholic steatohepatitis borderline (NASH). NAFL with mild inflammation progresses to NASH, fibrosis, cirrhosis, and, consequently, hepatocellular cancer (HCC). In the context of therapeutic response or dietary modifications, steatosis and NASH seem to be quite dynamic and reversible. Whether liver cirrhosis and fibrosis are present or not, NASH and NAFL can lead to liver cancer. In some cases, NASH can induce liver cancer by generating varied degrees of fibrosis (fibrosis stages F1—F3) and cirrhosis (F4). Fibrosis (F1—F3) development owing to NASH is more prevalent (34—42%) than fibrosis reversal (18—22%). Depending on the illness stage, the incidence of HCC might range from 2.4% to 12.8% (with or without cirrhosis).[37]

Our data showed that sensitivity analysis of liver stiffness measured by transient elastography (FibroScan) can be used to discriminate between the liver cirrhosis cirrhotic group and the HCC group at a cutoff level of>24.3, with 90.5% sensitivity, 85.7% specificity, 86.4% PPV, and 90% NPV (AUC = 0.941 and P value less than 0.001).

These findings were comparable to ones reported by Ebrahim et al.,[10] who highlighted that liver stiffness values > 24 kPa in hepatitis C virus patients can significantly predict HCC presence with a sensitivity of 98.2%, specificity of 83.8%, PPV of 94.5%, NPV of 77.3%, and overall diagnostic accuracy of 89%.

Another study conducted by Tatsumi et al.[2] reported that liver stiffness exceeding 12 kPa was an independent risk factor for the incidence of HCC.

Determining the optimal cutoff for HCC occurrence would be useful in evaluating HCC risks.

Rinaldi et al.[38] conducted a cohort study and followed up 258 HCV-positive patients till the development of HCC, and conducted a sensitivity analysis. The results showed that FibroScan can significantly predict HCC among HCV-positive patients using a cutoff value of liver stiffness measurement of 27.8 kPa showed 72% sensitivity and 65% specificity, and an AUC of 69.1%, with a P value of 0.0001.

As well, Masuzaki et al.[13] demonstrated a 45.5 times elevated HCC risk in patients with liver stiffness >25 kPa in comparison to cases with TE < 10 kPa.[39] Alder et al. revealed an elevated risk of HCC in cirrhotic patients with liver stiffness value > 30 kPa.

One strength point within this research is that it showed a large sample size of both cirrhotic and HCC patients. We faced a few limitations of being single-center study, and results cannot be generalized over the whole region. There is scarcity of evidence regarding the optimal cutoff point for liver stiffness to diagnose HCC.

4.1. Conclusion

FibroScan can significantly predict HCC among patients post-HCV treatment using a cutoff point of liver stiffness >24.3 kPa.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article.

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Conflicts of interest

There are no conflicts of interest.

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