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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, a number of noninvasive diagnostic tools for assessing hepatic fibrosis as a risk factor for HCC, such as fibroscan.

Aim of the work: Assess the role of Transient Elastography (Fibroscan) in prediction of (HCC) in chronic hepatitis C virus patients.

Patients and Methods: A case-control study 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 taken, and thorough clinical examination, they were assessed for liver stiffness using fibroscan, all patients underwent Triphasic CT scan, routine laboratory investigations were taken from each patient as liver function test, CBC and tumor markers.

Result: Males resembled the majority and patients with HCC were significantly older than those without HCC (p-value < 0.001). Our data showed that sensitivity analysis of liver stiffness measured by transient elastography (FibroScan) can be used to discriminate between 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 & p-value less than 0.001).

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

Keywords: *HCC; Fibroscan; Liver stiffness; Cirrhosis.*

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INTRODUCTION

Liver cell carcinoma (HCC) is the fifth commonly diagnosed malignancy globally and the third main factor for cancer related mortality.[1-2] Because of the prominent incidence of 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 for HCC and 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 quantitative evaluation of liver fibrosis, unfortunately, liver biopsy is expressing many drawbacks 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 has been proposed for early diagnosis of primary liver tumors and follow-up of cirrhotic patients, Fibroscan became feasible to assess the elasticity of the 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 that liver stiffness measured by Fibroscan with risk for development of HCC in the European population [13]; however, the risk of HCC was extrapolated form the degree of cirrhosis measured by Fibroscan indicating that HCC-related liver stiffness couldn't be precisely evaluated [14].

Thus, our goal was to assess the role of Transient Elastography (Fibroscan) in prediction of (HCC) in chronic hepatitis C virus patients

PATIENTS AND METHODS

We conducted a case control study including 133 HCC patients, They were recruited from the multidisciplinary HCC clinic at Kasr-Alainy 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 the standards in the American Association's guidelines for the study of Liver Diseases (AASLD), using computerized tomography (CT) or magnetic resonance imaging (MRI) techniques and alpha-fetoprotein (AFP) [15]. Patients with other chronic liver diseases than HCV e.g., HBV, alcohol related, autoimmune liver disease and patients co-infected with HIV and HCC patients who receive any previous treatment to HCC were excluded form final analysis.

All studied patients were subjected to the following: Taking their history including Personal history such as (name, age, gender, occupation, residence and special habit of medical importance), 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, foetor 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 (Liver: size, border, surface, consistency, tenderness, pulsation, 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), Alpha-fetoprotein (AFP) was assessed using Latex Immunoturbidimetric Method, and Viral hepatitis markers including (HCV Ab, HBVs Ag) using ELISA technique.

Pelviabdominal Ultrasound was done by the same operator for all patients for examination of liver echotexture & 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 abdomen and pelvis was done to diagnose and 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 on the right hepatic lobe through intercostal spaces. The probe's transducer tip was placed between the ribs and coated with coupling gel. The operator detected a portion of the liver free of large vascular structures and distant from HCC with the help of an ultrasonic time-motion imaging. Each subject 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 greater than 14 kPa, histology, and radiographic or endoscopic indications of portal hypertension [17].

Sample size: we used a convenient period sampling, it included all eligible patients who were assessed in the multidisciplinary HCC clinic at Kasr-Alainy Hospital during the period from Feb 2022, till Aug 2022.

Ethical considerations: study protocol was reviewd and approved by the ethical committee of AlAzhar university (Ethical approval number, 000089).

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 the mean, standard deviation, median, minimum, and maximum; categorical data were described using frequency (count) and relative frequency (%). The non-parametric Kruskal-Wallis and Mann-Whitney tests were used to compare quantitative variables. In order 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 statistically significant.

RESULTS

A case control study included 133 patients with liver cirrhosis and 133 patients with HCC was conducted.

		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		

Table 1: Basic characteristics of the studied groups Patients with HCC were significantly older in age and the majority of them were males (p-value < 0.001). The studied groups did not differ with regard to their weight, height or BMI.

		Groups				P-value
		Liver cirrhosis group		HCC group		
Diabetes mellitus		3	2.3%	5	3.8%	0.473
Cigarette Smoking	Non-smoker	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%	٣٢	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%	

Table 2: Comparisons between studied groups as regard medical history Patients with HCC were far more likely to smoke cigarettes (p-value 0.003). 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).

		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 3: Comparisons between studied groups as regard abdominal examination There were highly statistically significant difference between studied groups as regard liver and spleen size (p-value < 0.001) the groups did not differ regarding the presence of ascites (p-value > 0.05).

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 4: radiological characteristics of hepatic lesions among the HCC group.

In the current study, most of HCC lesions were solitary accounting for 55.6%, followed by >3 lesions in 24.8%, then 2 lesions in 15.8% and 3 lesions in 3.8%, with mean size of all lesions 4.25 ± 2.45 cm.

	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)	.69	.10	7.00	1.20	.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	.90	1.67	1.3	1.00	2.11	-8.730	**<0.001**
AFP (ng/ml)	3.5	.50	77.28	62.5	2.3	61344.0	-10.96	**<0.001**

Table 5: Laboratory characteristics of the studied groups. Patients with HCC had significantly lower hemoglobin level and platelet count and higher white blood cells count as compared to 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).

		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		

Table 5: Comparisons between studied groups as regard steatosis grade, CAP and liver stiffness measurements. 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 to 66.2% of patients without HCC. On the opposite side, patients with HCC had significantly higher liver stiffness as compared to patients without HCC (p-value < 0.001).

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

Table 6: Diagnostic performance of FibroScan in discrimination of liver cirrhosis and HCC in chronic HCV patients.

Using ROC curve, it was shown that FibroScan can be used to predict HCC using cutoff level of > 24.3, with 90.5% sensitivity, 85.7% specificity, 86.4% PPV and 90% NPV (AUC = 0.941 & p-value < 0.001) (table 6, figure 1).

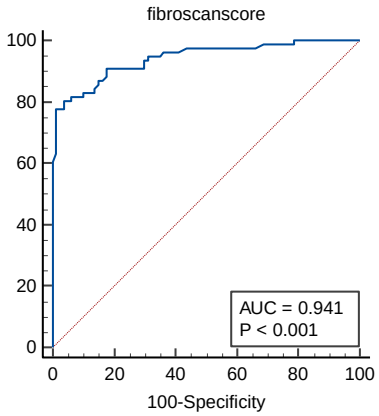

Fig. 1: ROC curve of FibroScan in discrimination of liver cirrhosis cirrhotic group and HCC group

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].

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 case-control research to assess the role of Transient Elastography (Fibroscan) in 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 HCC group was significantly older in age 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 reported in literature that revealed old age, male gender, and cigarette smoking were correlated with a higher risk for development of HCC. HCC incidence peaks at the age of seventy, while cases before the age of forty 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 2:1 and in some countries 4:1 [24], some reports showed that males not only having higher incidence but also higher relapse rate [25].

However, findings in our were inconsistent with the study was done by Ebrahim et al.,[10] who conducted a case control study including 25 cirrhotic patients and 25 HCC patients and results showed that HCC group had significantly higher BMI while age and gender was not significantly different. Reasons for this include the small sample size of the later research compared to the current one.

Regarding liver and spleen size, there was a remarkable statistical significance difference between the analyzed groups in the current study (p-value < 0.001). our results are consistent with large cohort study that stated 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 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 conducted by Ebrahim et al.,[10] who stated that 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 cells count as compared to 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 literature stating that erythropoietin and Thrombopoietin are produced by liver and kidneys, it stimulates the production and differentiation of megakaryocytes into mature platelets. During liver cirrhosis and advancing in HCC a marked decline of those factors has been reported leading to anemia and low platelet count [28-30].

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

In the present study, total bilirubin and INR are one of the components for classification of Child-Pugh classification and BCLC classification, elevated total bilirubin and/or bilirubin indicates advanced stages of HCC, this 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 to 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 to 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 to those with no steatosis, those with steatosis had a 2.81-times higher likelihood of getting HCC.

Sedentary lifestyle and imbalanced dietary calories lay the foundation for nonalcoholic fatty liver (NAFL), which can evolve to 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 led 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 liver cirrhosis cirrhotic group 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 & 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 sensitivity 98.2%, specificity 83.8%, PPV 94.5%, NPV 77.3%, and overall diagnostic accuracy 89%.

Other study conducted by Tatsumi et al., [38] 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., [39]conducted a cohort study and followed up 258 HCV positive patients till development of HCC, and conducted a sensitivity analysis, results showed that Fibroscan can significantly predict HCC among HCV positive patients using a cutoff value of liver stiffness measurement 27.8 kPa, showed 72% sensitivity and 65% specificity and AUC 69.1%, with p value 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 [40]. 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 few limitations of being single center study, and results can't be generalized over the whole region, there is scarcity of evidence regarding the optimal cutoff point for liver stiffness to diagnose HCC.

CONCLUSION

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

Conflict of interest : none

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