The sensitivity of different non-invasive methods in diagnosis of liver fibrosis in chronic hepatitis C virus patients

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Abstract: Background: Hepatitis C virus infection is associated with a wide spectrum of liver disease. Evaluation of stage of liver fibrosis is of therapeutic and prognostic importantance, the non-invasive methods are needed o replace the invasive liver biopsy. Aim of work: The study aimed to measure the sensitivity of the non-invasive Fibrotest, Fibroscan and ultrasonography in diagnosis of hepatic fibrosis secondary to chronic hepatitis C infection. Material and Methods: 80 HCV positive patients participated in the study all are subjected to, abdominal ultrasonography, fibrotest (total bilirubin, gamma-glutamyltransferase, alpha-2 macroglobulin, haptoglobin, alanine aminotransferase, and apolipoprotein-A1), liver stiffness measurement using fibroscan and liver biopsy (assessed for the stage of hepatic fibrosis using METAVIR staging of fibrosis or scarring). Results: 66 were men (82.5%) and 14(17.5 %) were females, the median age was 51 ± 12. According to liver biopsy, 32 patients diagnosed as cirrhotics (F4) and 48 patients were diagnosed as non cirrhotics (F0-F1-F2-F3) [25]. The closest results to liver biopsy was that of fibroscan that showed 32 patients were cirrhotics and 48 patients were non cirrhotics, with sensitivity/specificity 100/100%. These results followed by that of fibrotest 44 patients were cirrhotics and 36 patients were non cirrhotics with sensitivity/specificity 100/75%. Conclusion: the non-invasive methods, specifically fibroscan, as sensitive as liver biopsy in diagnosis of liver fibrosis secondary to chronic hepatitis C, but the sensitivity is higher in advanced stages of fibrosis and cirrhosis.

Introduction:

Hepatitis C virus (HCV) infection is associated with a wide spectrum of liver disease. In 1999, the World Health Organization estimated the global prevalence of HCV infection to be approximately 3%, with the disease affecting around 170 million people [1]. Progressive fibrosis ending in cirrhosis is the hallmark of worsening chronic hepatitis C infection (CHC). Complications of end-stage liver disease, as a result of cirrhosis, including liver failure, ascites, variceal bleeding, porto-systemic hepatic encephalopathy and hepatocellular carcinoma.

At presentation, 10–20% of chronic hepatitis C patients are cirrhotic and between 20% and 30% of noncirrhotic patients will develop it within one or more decades [2-4].

Liver biopsy (LB) was previously the acceptable method to evaluate the severity of hepatic fibrosis in patients with chronic hepatitis C infection. However, LB is expensive and associated with a risk of severe complications. Therefore, noninvasive tests have been developed to assess the severity of liver fibrosis [5,6]. Moreover, inadequate sample size and heterogenisity of liver fibrosis in HCV can lead to significant bias in the assessment of hepatic histology [7].

The noninvasive approaches employing ultrasound-based technology, including transient elastography (TE)-FibroScan [8-10], real-time elastography (10-14), and acoustic radiation force impulse elastography (ARFI) [16-20], and serological methods, most notably, FibroTest-ActiTest, became promising for evaluation of liver fibrosis [21].

lipid profile(total cholesterol, LDL, HDL and TG), liver profile (AST, ALT, serum bilirubin, Alk. phosphatase, total protein, serum albumin and prothrombin time(INR)and alpha-fetoprotein, Viral hepatitis serology (HCV Ab, HCV RNA). Autoimmune markers (ANA, AMA, ASMA, LKM).

Aim of work: The study aimed to measure the sensitivity of the non-invasive Fibrotest, Fibroscan and ultrasonography in diagnosis of hepatic fibrosis secondary to chronic hepatitis C infection.

Material and methods:

1. Study subjects:

The population of the study derived from HCV infected patients attending Ain-Shams University hospital. The sample included 80 patients all had an indication for liver biopsy (LB). The study protocol was consistent with the ethical guidelines of Helsinki. Written informed consent was obtained from each

participant or responsible family members after the possible complications of LB had been fully explained. All participants subjected to full history taking, thorough clinical examination, and measurement of body mass index (BMI). All the following criteria included: serum alanine aminotransferase (ALT) levels >1.5 the upper normal limit, either persistently or intermittently, in the presence of serum markers of infection with hepatitis C. Patients with ascites, hepatocellular carcinoma, high body mass index or those having too narrow intercostal space were excluded.

2. Laboratory tests:

Standard laboratory assessments: serum creatinine, blood urea nitrogen, Na, K, fasting and two hours postprandial blood glucose, volume is at least 100 times bigger than a biopsy sample and therefore is far more representative of the hepatic parenchyma.

The technique was performed by the same blinded gastroenterologist and at least 10 validated measurements were carried out in each patient. Measurements were performed on the right lobe of the liver through the intercostals spaces on patients lying in the dorsal decubitus position with the right arm in maximal abduction. The median value (expressed as kilopascals, kPa) was kept as representative of the liver elastic modulus.

The procedures were performed by an investigator who was blinded to the clinical, serological and histological data. On the right lobe of the liver, through intercostal spaces with the patient lying in dorsal decubitus with the right arm in maximal abduction, the tip of the transducer probe was covered with coupling gel and placed on the skin, between the rib bones at the level of the right lobe of the liver. The operator, assisted by a time-motion ultrasound image, located a liver portion at least 6-cm thick and free of large vascular structures. When the target area has been located, the operator pressed the probe button to commence the measurements. The measurement depth was between 25 and 65 mm. Ten validated measurements were performed on each patient. The success rate was calculated as the number of validated measurements divided by the total number of measurements. The results were expressed in kilopascals (kPa). The median value was considered representative of the elastic modulus of the liver (degree of fibrosis). The whole examination of each patient lasted less than 5 minutes. Only procedures with 10 validated measurements and a success rate of at least 65 % were considered reliable. The cut-off point of >65% for the success rate was chosen to maximize the consistency of the results for TE reproducibility. In addition, the median value of successful measurements was considered as representative of the liver stiffness in a given patient

only if the interquartile range (IQR= dispersion range) of all validated measurements was <30% of median values [24,28].

Interpretation of results of fibroscan:

Results of fibroscan are given in kilopascal grading from 0 – 75 kpa, whereas, patients with fibroscan results less than 13 kpa are non cirrhotics (f0- f1- f2- f3), but in cirrhotic patients liver stiffness.

All biopsy specimens were analysed independently by the same pathologist. According to the METAVIR scoring system. Fibrosis was staged on a 0-4 scale: F0, no fibrosis; FI, portal fibrosis without septa; FII, portal fibrosis and few septa extending into lobules; FIII, numerous septa extending to adjacent portal tracts or terminal hepatic venules; and FIV, cirrhosis [27].

3. Abdominal ultrasound:

Was done for all patients using a color doppler ultrasonic instrument. Grayscale and Doppler ultrasonography (DS) were performed by a Hitachi EUB 525 for all patients during the week prior to liver biopsy, with a 7.5 MHz linear and 3.5 MHz curved probes for grayscale US and a 3.5 MHz curved probe for DS.

The patients fasted for 6 hours prior to examination, and then were studied in supine and left posterior oblique positions. The radiologist performed the examination measured spleen and liver sizes; diameters of portal vein, intrahepatic veins, and splenic vein; and gallbladder wall thickness were measured in millimeters. Liver surface and hepatic parenchyma echogenicity were also recorded during grayscale US. Doppler parameters such as portal and hepatic vein blood velocities and directions, and wave patterns of blood flow were studied [25].

4. Liver biopsy:

Percutaneous Liver biopsy was performed under ultrasound guidance using 16-gauge needles. Specimens of at least 2.5 cm in length, including a minimum 12 portal tracts, Thin serial sections (4 micrometers [mcm] thick) from formalin-fixed, paraffin-embedded blocks of core liver biopsies were stained with hematoxylin & eosin (Hx & E) then assessed for the stage of hepatic fibrosis using METAVIR staging of fibrosis or scarring [26].

F0: No scarring.

F1: Minimal scarring.

F2: Scarring has occurred and extends outside the areas in the liver that contains blood vessels.

F3: Bridging fibrosis is spreading and connecting to other areas that contain fibrosis.

F4: Cirrhosis or advanced scarring of the liver.

Fibrotest which a simple non-invasive panel of biochemical markers for fibrosis, it includes data concerning five-biochemical markers (alpha-2macrogloulin, haptoglobin, gamma glutamyl

transpeptidase (GGT), total bilirubin and apoliporotein A), it has a good correlation with fibrosis stage [22].

Liver stiffness measurement (LSM) using FibroScan was introduced as a noninvasive device to accurately assess liver fibrosis [23]. Liver stiffness measurement using fibroscan is reproducible and independent of the operator and explores a volume of liver parenchyma which can be approximated to a cylinder of 1 cm in diameter and 4 cm in length. This volume is 100 times larger than the biopsy specimen volume and is thus much more representative of the entire hepatic parenchyma[24].

5. Serum fibrosis markers:

Markers of liver fibrosis were assessed at the time of liver biopsy. Fibrotest (FT): five parameters (total bilirubin, gamma-glutamyltransferase, alpha-2 macroglobulin, haptoglobin, and apolipoprotein-A1) were evaluated and the FibroTest score was computed from the Biopredictive website (www. Biopredictive.com). The following formula (equation) is available on the patients for diagnosing the degree of fibrosis by FT: F = 4.467 x log [alpha2-macroglobulin g/L)] – 1.357 x log [haptoglobin (g/L)] + 1.017 x log [gamma-glutamyl transpeptidase (IU/L)] +.0281 x [age (in years)] + 1.737 x log [bilirubin (Mmol/L)] – 1.184 x [apolipoprotein A 1 (g/L)] + 0.301 x sex (female = 0, male = 1) – 5.540. It has a score ranging from 0.0 to 1.0 [27].

6. Liver Stiffness Measurement by Fibroscan:

All patients were studied using the non-invasive method of transient elastography. It uses both ultrasounds of 5 MHz and low frequency elastic waves. The system consists of a probe with an ultrasonic transducer mounted on the axis of a vibrator. This vibrator induces a wave of mild amplitude and low frequency to the tissue. Thus, an elastic shear wave is created that propagates in the tissue and in the meantime a pulse-echo ultrasound is performed to follow the shear wave and measures its velocity. The velocity of propagation is directly related to the tissue stiffness. The harder the tissue, the faster the shear waves propagates[11,17].

Measurements are totally non-invasive and performed on the right lobe of the liver through intercostals spaces between 25 and 45 mm from the skin surface. For each patient, the obtained elasticity value is the median of several measurements (usually 10) and the results are expressed in kilopascals (kPa). Transient elastography measures the liver stiffness in a volume that approximates a cylinder 1-cm wide and 4-cm long. This

Ten patients (12.5%) with fibrosis F0-F1 (METAVIR score) by biopsy showed a mean Fibroscan score of 5.2 kPa (range, 2.3-6.8 kPa). 38 patients (47.5%) exhibited F2-3 by biopsy with a mean Fibroscan score of 10.8 kPa (range, 8.9-12.7 kPa). The last 32 patients (40%) with F4 (cirrhosis) by biopsy and abnormal clinical data showed the highest mean Fibroscan value of 14.2 kPa (range, 8.9-18 kPa).

The ultrasonography results showed that 18 patients were cirrhotics and 62 patients were non cirrhotics. The results of the fibrotest showed that 44 patients were cirrhotics and 36 patients were non cirrhotics. In addition to the fibroscan that showed 32 patients were cirrhotics and 48 patients were non cirrhotics ranges from 13- 15 kpa to 75 kpa. Interpretation of these results is written in the fibroscan report in correlation with the METAVIR histological index of grading fibrosis (f 0- f 1- f 2- f 3- f 4) [24].

7. Statistical methods:

The data were collected, revised, verified then edited on personal computer. The data was analyzed by the aid of program (SPSS) for windows version 15.2, 2004, USA. Using the following tests: Chi-square, Student "T", ANOVA, Diagnostic validity, ROC curve. p value of >0.05 is considered non significant. p value of <0.05 is considered significant. p value of <0.001 is considered highly significant.

Results:

Among 80 patients, with hepatitis C virus infection, 66 were men (82.5%) and 14(17.5 %) were females, the median age was 51 ±12. According to the results of liver biopsy, the subjects were divided into: 10 patients Stage 0,1 (Mild fibrosis). 38 Stage 2,3 (Moderate fibrosis). 32 Stage 4 (Severe fibrosis) i.e. 32 patients diagnosed as cirrhotics (F4) and 48 patients were diagnosed as non cirrhotics (F0-F1-F2-F3).

Table(1) A comparison between patients with mild, moderate and severe fibrosis as regards liver function tests and results of fibroscan.

	Mild Fibrosis(10) (X ± SD)	Moderate fibrosis(38) (X ± SD)	Severe fibrosis(32) (X ± SD)	ANOVA	sig
WBCs	6.6 ± 2.1	7.1 ± 2.1	5.5 ± 2.0	1.263	>0.05
Hb	14.3 ± 1.6	15.3 ± 4.4	12.2 ± 2.4	1.541	>0.05
Plt	232.3 ± 49	215.1 ± 83	115.1 ± 31	12.49	<0.01
ALT	42.0 ± 27.8	48.4 ± 15.2	72.1 ± 49.4	2.787	>0.05
AST	34.3 ± 16.5	46.2 ± 22.6	80.8 ± 40.8	10.65	<0.01
ALP	165.1 ± 54	185.3 ± 82	229.5 ± 120	2.027	>0.05

	Mild Fibrosis(10) (X ± SD)	Moderate fibrosis(38) (X ± SD)	Severe fibrosis(32) (X ± SD)	ANOVA	sig
protein	7.7 ± 0.7	7.9 ± 0.8	7.4 ± 0.7	1.260	>0.05
Albumin	4.3 ± 0.3	3.9 ± 0.4	3.4 ± 0.8	12.23	<0.01
Total bilirubin	0.9 ± 0.4	1.1 ± 0.2	1.4 ± 0.8	3.909	<0.05
GGT	41.2 ± 26.4	33.1 ± 22.9	67.1 ± 13.2	5.056	<0.05
INR	1.0 ± 0.1	1.0 ± 0.1	1.2 ± 0.2	5.229	<0.05
Fibroscan	5.2± 2.56	10.8± 4.93	14.2± 8.21	37.691	<0.01

There is a highly significant increase in the liver stiffness measured by FibroScan among patients with mild, moderate and severe fibrosis (p=0.01).

Table (2) The sensitivity and specificity in different diagnostic modalities

	Clinical	U/S	Fibrotest	Fibroscan
Specificity	91.7	95.8	75.0	100.0
Sensitivity	62.5	50.0	100.0	100.0
P-	78.6	74.2	100.0	100.0
P+	83.3	88.9	72.7	100.0
Efficacy	80.0	77.5	85.0	100.0

P- negative predictive value. P+ positive predictive value.

The previous table represented that fibroscan gave the most equivalent results to that of liver biopsy

Table (3) Comparison between liver biopsy and Fibrotest in detection of liver cirrhosis:

Biopsy	Fibrotest		total	Chi-squre value	P value
	-ve	+ve			
-ve count, % of total	36 45.0%	12 15.0%	48 60.0%	21.818	.000
+ve count, % of total		32 40.0%	32		
Total count, %of total	36 45.0%	44 50.0%	80 100.0%		

The results of fibrotest were significantly matching that of liver biopsy (p=0.000).

Table (4) Comparison between fibroscan and liver biopsy in detection of liver cirrhosis.

Biopsy	Fibroscan		total	Chi-squre value	P value
	-ve	+ve			
-ve count, % of total	24 60.0%		48 60.0%	40.000	.000
+ve count, % of total		32 40.0%	32		
Total count, %of total	48 60.0%	32 40.0%	80 100.0%		

The results of fibroscan were significantly matching that of liver biopsy (p=0.000).

Table (5) Comparison between results of fibrotest and fibroscan in detection of liver cirrhosis

Fibrotest	Fibroscan		Total	Chi-squre value	P value
	-ve	+ve			
-ve count, % of total	36 45.0%		36 45.0%	21.818	.000
+ve count, % of total	12 15.0%	32 40.0%	22 55.0%		
Total count, %of total	48 60.0%	32 40.0%	80 100.0%		

The results of fibrotest were significantly matching that of fibroscan (p=0.000).

Davoudi et al. 2015, studied a total of 60 patients underwent investigation using gray-scale and Doppler ultrasonography, the sensitivity was 40% and specificity was 100%, accuracy was 0.682, positive predictive value and negative predictive value were 0.100 and 0.35 respectively[35].

In the present study there was a significant relation between US and liver biopsy in detection of cirrhosis (p=.001). However, *Choong et al. 2012,* stated that there was no significant correlation between ultrasound scores and the stage of fibrosis[34]. On the contrary, *D'Onofrio et al. 2005* found that correlation between B-mode US and histological scores was not statistically significant (Rs=0.45; p=0.0001)[33].

In the current study, the non invasive markers of hepatic fibrosis (FT) were evaluated and the results were as following: the sensitivity of the fibrotest was 100%, the specificity was 75%, negative predictive value was 100%, positive predictive value was 72.7%.

In a study for validation of fibrotest in assessing liver fibrosis *Imbert-Bismut, 2001* found that the sensitivity of fibrotest was 100%, the specificity was 21 %, negative predictive value was 100 %, positive predictive value was 50 %.

Imbert-Bismut agreed with the current study in the sensitivity and the negative predictive value but disagreed with the specificity and the positive predictive value whereas the present study was more specific and gave higher positive predictive value results[36]. *Enrico Rossi 2003* studied the validation of the fibrotest biochemical markers score in assessing liver fibrosis in hepatitis C patients, found the sensitivity of the fibrotest was 42%.

Discussion:

Accurate and safe non-invasive tests are needed to measures severity of liver fibrosis. There has been an increase in the number of noninvasive tests of liver fibrosis over the last decade some of which have been shown to have clinical utility[29-31]. Clinicians must choose between different serological tests and elastographic methods[32].

This study evaluated the performance of non-invasive fibrotest, fibroscan and ultrasonography compared to liver biopsy in 80 consecutive patients with CHC. The diagnostic performance of each test was good, the ultrasonographic results compared to liver biopsy results was as following: the specificity was 95.8 %, sensitivity was 50 %, efficacy was 77.5 %, positive predictive value was 88.9 and the negative predictive value was 74.2. A prospective study done by *D'Onofrio et al. 2005*, 105 patients (32 F, 73 M) affected by chronic viral liver disease in 36 months, Patients were studied with B-mode US and then underwent US-guided liver biopsy. US identification of liver fibrosis in chronic liver disease gave 25%

sensitivity, 100% specificity, 100% positive predictive value and 79% negative predictive value, with an 80% diagnostic accuracy[33].

A study by *Choong et al. 2012*, a retrospective evaluation of the ultrasound images of 156 patients with chronic viral hepatitis who underwent liver biopsy was performed. Cirrhosis was present in 23 patients (14.7%). Surface nodularity had the best sensitivity of 74% with an accuracy of 65%. However, the score for surface + texture combination had the best accuracy (67%) for detection of cirrhosis. Combined score had the best positive predictive value of only 31%. Surface nodularity had the highest negative predictive value of 93%[34] (p=0.000).

These results nearly the same that obtained by *Simona Bota et al. 2011*, studied a new scoring system for prediction of fibrosis in chronic hepatitis C, they found a highly significant correlation between fibroscan and degree of liver fibrosis (assessed according to METAVIR score) by LB (p=0.0001)[42].

We compared between the different methods regarding the sensitivity and specificity in the diagnosis of liver cirrhosis was as the following: U/S sensitivity/specificity 50.0/95.8, fibrotest sensitivity/specificity 100.0/75.0, fibroscan sensitivity/specificity 100.0/100.0.

Shaheen AA et al. 2007 compared FibroTest or FibroScan versus biopsy in HCV patients were identified via an electronic search.At a threshold of approximately 0.60, the sensitivity and specificity of the FibroTest were 47% (35-59%) and 90% (87-92%). For FibroScan (threshold approximately 8 kPa), corresponding values were 64% (50-76%) and 87% (80-91%), respectively[43].

Pyonard et al. 2012 studied a total of 1289 patients with CHC and 604 healthy volunteers, with assessment of fibrosis stage by three techniques (fibrotest, liver stiffness by fibroscan, and liver biopsy), and alanine aminotransferase (ALT) taken as a control test, they found the sensitivity and specificity of the three techniques in diagnosis of cirrhosis as the following: FibroTest 0.87/0.41, LSM 0.93/0.39, ALT 0.78/0.08 and biopsy 0.95/0.51. The analysis of the discordances between pairs suggested that the variability of the model was mainly related to the discordances between biopsy and LSM (residuals>10; p<0.0001)[44]. The difference in results may be due to the number of patients taken in the studies compared to the present one.

On the other hand, fibroscan and fibrotest are highly matched in the positive results in detection of liver fibrosis (p=0.00).

Friedrich-Rust et al. 2010, studied retrospectively seventy four patients with chronic liver disease, who received a liver biopsy, transient elastography (TE) and the FibroTest using histology,

they found correlation coefficient between TE (transient elastography) and FibroTest was 0.67 (p < 0.0001)[45].

Also, in the study we have mentioned that there was a highly significant increase in liver stiffness measured by fibroscan in patients 94%, negative predictive value was 85 % and positive predictive value was 78 % [37]. The disagreement in both studies may be due to the difference in etiology of liver disease in as including alcohol intake increases the blood level of the fibrotest parameters (as alpha-2 macrogloulin, haptoglobin, gamma glutamyl transpeptidase GGT) even without fibrosis.

The diagnostic performance of fibroscan, as a non invasive method of liver fibrosis assessment, in comparison to LB was as the following: the sensitivity was 100 %, the specificity was 100 %, positive predictive value was 100 %, negative predictive value was 100 % and the efficacy was 100 %.

In a study by *Talwalkar J.A, et al. 2007*, the diagnosis of cirrhosis with fibroscan was as following: sensitivity was 87%, specificity was 91% the positive predictive value was 95% and the negative predictive value was 95%. Thus, TE appears to be an excellent tool for the early detection of cirrhosis, whatever the causal disease [38].

In another prospective studies of patients with chronic hepatitis C by *Saito 2004* and *Ziol, 2005* for assessing diagnostic accuracy of fibroscan, they found 87% for sensitivity and 97% for specificity [39, 40].

In a study by *Foucher et al. 2006*, for patients with CLD with varying aetiology, they suggested that TE (transient elastography) has a good diagnostic accuracy in identifying advanced fibrosis (F3) or cirrhosis (F4), but the assay was less accurate for prediction of moderate liver fibrosis. In fact, in three large series of patients with CLD, the range of diagnostic accuracy of TE was 87% for sensitivity and 97 % for specificity[41].

These studies are in agreement with the current study in the specificity, positive predictive value and negative predictive value, but this study gave higher sensitivity results and this discordance in the sensitivity results may be due to the specific selection of the patients shared in this study, as we excluded those with ascites and high body mass index.

The present study showed a highly significant relation (85%) between results of liver biopsy and fibroscan in detection of liver cirrhosis a prospective study on the incidence and hierarchy of major complications with severe fibrosis (as shown in table 1, p<0.01). Again the sensitivity of fibroscan in detection of advanced liver fibrosis and cirrhosis in comparison to biopsy was high (table 5)(p=0.000).

This was in agreement with *El-Saadany S et al. 2016* who studied the results of fibroscan and biopsy in 348 CHC patients and they with severe fibrosis (as shown in table 1, p<0.01). Again the sensitivity of fibroscan in detection of advanced liver fibrosis and cirrhosis in comparison to biopsy was high (table 5) (p=0.000).

This was in agreement with *El-Saadany S et al. 2016* who studied the results of fibroscan and biopsy in 348 CHC patients and they found that biopsy correlated positively with fibroscan data in moderate fibrosis (p < 0.001), but not in mild or no fibrosis (p = 0.12) and they concluded that Fibroscan correlated with fibrosis degree in liver biopsy and can be used as noninvasive tool to diagnose moderate (F2– F3), but not mild (F1) fibrosis[46].

The previous results in addition to other studies suggested that the diagnostic performance of the non-invasive abdominal ultrasonography, fibrotest and fibroscan for detection of fibrosis related HCV is high, the sensitivity and specificity are higher in detection of advanced liver fibrosis and cirrhosis.

In conclusion: the non-invasive methods, specifically fibroscan, as sensitive as liver biopsy in diagnosis of liver fibrosis secondary to chronic hepatitis C, but the sensitivity is higher in advanced stages of fibrosis and cirrhosis.

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