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Original article

Comparison between Transient Elastography (FibroScan) and Liver Biopsy for the Diagnosis of Hepatic Fibrosis in Chronic Hepatitis C Patients

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Abstract:
Transient elastography (TE) is gaining popularity as a non-invasive method for predicting liver fibrosis. The practical utility of the method is based on establishing cutoff values for each stage of fibrosis. A diagnosis of stage is based on measurements of liver stiffness that vary in different studies. The present study aimed to establish cutoff values for each stage of fibrosis to assess the performance of TE in fibrosis staging in Egyptian chronic HCV patients. This cross-sectional study was conducted at Specialized Medical Hospital and the Egyptian Liver Foundation, Mansoura, Egypt. The inclusion criteria were: age older than 18 years and chronic infection by hepatitis C. The exclusion criteria were the presence of ascites, pacemaker or pregnancy. Three hundred and fifty six consecutive patients with chronic hepatitis C participated in the study. Liver fibrosis was staged according to the METAVIR system. The AUROCs for F2 or greater, F3 or greater and cirrhosis (F4) were 0.91 (95% CI 0.87 to 0.94), 0.95 (95% CI 0.91 to 0.99) and 0.97 (95% CI 0.96 to 0.99), respectively. ROC curve analysis identified optimal cutoff value of liver stiffness measurements as high as 9.8 kPa for F ≥ 2, 10.4 kPa for F ≥ 3, and 17.2 kPa for F = 4. The overall relation between fibrosis stages when comparing both FibroScan and biopsy was significant agreement between both (the kappa measure was 0.430 and p<0.001). TE is a good non-invasive tool for diagnosis and monitoring of liver fibrosis among patients with Chronic HCV infection.

Keywords:
Transient elastography
FibroScan
Liver biopsy
Chronic hepatitis C

Abbreviations: *ALT*; Alanine Transaminase. *AST*; Aspartate Transaminase. *AUROC*; Area Under Receiver Operator Characteristic Curve. *BMI*; Body Mass Index. *CHC*; Chronic Hepatitis C. *CI*; Confidence Interval. *HCV*; Hepatitis C Virus. *Hgb*; Hemoglobin. *IQR*; Inter Quartile range. *kPa*; Kilo Pascal. *LSM*; Liver Stiffness Measurement. *NPV*; Negative Predictive Value. *PCR*; Polymerase Chain Reaction. *PPV*; Positive Predictive Value. *ROC*; Receiver Operator Characteristic Curve. *SD*; Standard Deviation. *SPSS*; Statistical Package for Social Sciences. *TE*; Transient Elastography. *WBCs*; White Blood Cells.

Conflict of interest: The authors who have taken part in this study declared that they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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1. Introduction

The accurate diagnosis of chronic hepatitis C (CHC) related fibrosis is crucial for prognosis and treatment decisions, and is currently best evaluated by histological examination of liver biopsy [1,2]. However, liver biopsy has several disadvantages, including poor patient compliance, sampling errors, limited usefulness for dynamic follow-up, and a risk of complications typical of invasive procedures. In addition, the predictive power of histology may be weakened by sampling variability [3-7]. Together, these constraints of liver biopsy have encouraged the search for non-invasive methods to assess progression of fibrosis. The ideal noninvasive technique should be valid, painless, reproducible, easy-to-learn, easy-to-perform and cheap. There is an interest in developing methods, either serological or imaging, which are all non-invasive, in order to determine the presence and degree of fibrosis. Among these new techniques are serum markers and unidimensional transient elastography (FibroScan). Transient elastography (TE) using FibroScan is a relatively new, noninvasive, and reproducible technique that evaluates tissue stiffness. Liver stiffness measurement (LSM) has been demonstrated to be a reliable tool for assessing hepatic fibrosis and cirrhosis, especially in patients with chronic hepatitis [8-12]. Studies performed on a large number of HCV patients indicate that the LSM is highly correlated with the stage of fibrosis. The practical utility of the method is based on establishing cutoff values for each stage of fibrosis. A diagnosis of stage F ≥2, F ≥3 and F4 (cirrhosis) is based on measurements of liver stiffness that vary, according to some studies, from 6.2 to 8.8 Kpa, 7.7 to 10.8 kPa and from 11 to 16.3 kPa, tab. (1). This method should be locally evaluated, as circulating virus genotype (genotype 4), increased body mass index highly prevalent in Egypt, and co-infections with schistosomiasis may interfere with liver fibrosis assessment. The present study aimed to establish cutoff values for each stage of fibrosis to assess the performance of TE in fibrosis staging in Egyptian chronic HCV patients.

Table (1) Diagnostic accuracy of TE in different published reports that used only patients with CHC

Fibrosis Stage	Author	Cutoff (kPa)	Se (%)	Sp (%)	PPV (%)	NPV (%)	AUROC
F≥2	Ziol et al., 2005 [8]	08.8	56.0	91.0	56.0	88.0	0.79
	Castera et al., 2005 [9]	07.1	67.0	89.0	48.0	95.0	0.83
	Sporea et al., 2008 [13]	06.8	59.6	93.3	98.0	30.1	0.773
	Arena et al., 2008 [14]	07.8	83.0	82.0	83.0	79.0	0.91
	Nitta et al., 2009 [15]	07.1	82.8	80.3	86.0	73.6	0.88
	Rizzo et al., 2011 [16]	06.5	71.0	71.0	82.0	56.0	0.78
	Kim et al., 2011 [17]	06.2	76.0	97.5	97.4	80.0	0.909
	Ferraioli et al., 2012 [18]	06.9	71.7	91.4	87.8	79.0	0.88
	Shiha et al., 2014 [19]	8.55	65.95	84.43	70.1	81.7	0.86

F≥3	Ziol et al., 2005 [8]	09.6	86.0	85.0	93.0	71.0	0.91
	Castera et al., 2005 [9]	09.5	73.0	91.0	81.0	87.0	0.90
	Arena et al., 2008 [14]	10.8	91.0	94.0	92.0	73.0	0.99
	Nitta et al., 2009 [15]	09.6	87.7	82.4	72.5	92.7	0.90
	Rizzo et al., 2011 [16]	08.8	77.0	85.0	77.0	85.0	0.83
	Kim et al., 2011 [17]	07.7	100	95.7	87.5	100	0.993
	Ferraioli et al., 2012 [18]	07.3	91.7	88.3	75.0	96.5	0.95
	Shiha et al., 2014 [19]	10.2	83.70	89.23	62.6	96.22	0.919
F4	Ziol et al., 2005 [8]	14.6	86.0	96.0	97.0	78.0	0.97
	Castera et al., 2005 [9]	12.5	87.0	91.0	95.0	77.0	0.95
	Arena et al., 2008 [14]	14.8	94.0	92.0	73.0	98.0	0.98
	Nitta et al., 2009 [15]	11.6	91.7	78.0	41.5	98.2	0.90
	Rizzo et al., 2011 [16]	11.0	70.0	82.0	53.0	90.0	0.80
	Kim et al., 2011 [17]	11.0	77.8	93.9	58.3	97.5	0.970
	Masuzaki et al, 2011 [18]	15.9	78.9	81.0	87.2	69.4	0.87
	Ferraioli et al., 2012 [20]	09.3	95.8	93.4	76.7	99.0	0.97
	Shiha et al., 2014 [19]	16.3	100.0	90.62	27.7	100.0	0.966

2. Patients and Methods

2.1. *Study design*

This cross-sectional study was conducted at Specialized Medical Hospital and the Egyptian Liver Foundation, Mansoura, Egypt. The inclusion criteria were: age older than 18 years and chronic infection by hepatitis C, characterized by the presence of HCV-RNA in blood serum. The exclusion criteria were the presence of ascites, pacemaker or pregnancy. Three hundred and fifty six consecutive patients with chronic hepatitis C participated in the study. Therefore, 356 pairs of exams were done by two operators at the same day. Both operators have realized more than 500 exams previously, being classified as experienced operators [21]. The LSM value used in this analysis was the mean of the two readings.

2.2. *Ethical Considerations*

This study protocol was conducted in accordance with the Helsinki Declaration, and was approved by Mansoura Faculty of Medicine Ethics Committee. All patients signed an informed consent upon enrolment in this study.

2.3. *Transient elastography (TE*

The procedures were performed by two independent investigators (MA and RS) on the same day. The right lobe of the liver was accessed through an intercostal space while the patient was lying down in the dorsal decubitus position with the right arm in maximum abduction position. Using the FibroScan (Echosens, Paris, France) guide, a portion of liver of at least 60 mm in thickness, free of large vessels, was identified for examination. The rate of successful measurement was calculated as the ratio between the numbers of validated to total measurements. The results were expressed as a median value of the total measurements in kilo Pascal (kPa). TE was considered reliable when the following criteria had been met: (i) 10 successful measurements; (ii) an interquartile range (IQR) lower than 30% of the median value; and (iii) a success rate of more than 60% [22]. Liver stiffness was considered as the median of all valid measurements.

2.4. *Liver biopsy*

Liver biopsy specimens were obtained under complete aseptic procedures to retrieve 15 mm core or at least 15 portal tracts. The specimen was processed and stained with hematoxline and eosine. Fibrosis was staged on a 0–4 scale: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis and few septa; F3, numerous septa without cirrhosis; and F4, cirrhosis according to METAVIR scoring system [23].

2.5. *Statistical analysis*

Statistical analyses were performed using version 21, SPSS (Statistical Package for Social Sciences) (IBM Corp., USA). Continuous variables were reported as median (IQR). Categorical variables were reported as frequency (%). Significance level was determined when $P \leq 0.05$ assuming two tailed tests. The performance of TE was assessed with receiver operating characteristic (ROC) curves. A patient was considered positive or negative according to whether the noninvasive technique value was greater than, lesser than or equal to a given cut-off value. The ROC curve is a plot of sensibility vs (1-Specificity) for all possible cut-off values. The most commonly used accuracy index is the area under the ROC curve (AUROC), values close to 1.0 indicating high diagnostic accuracy. For each TE, sensibility and specificity were calculated for each threshold. The optimal cut-off values used for each test were determined by maximizing the Youden index (Se+Sp-1). Positive (PPV) and negative predictive values (NPV) were computed for these cut-off values. Agreement between results of liver biopsy and those of FibroScan was assessed by Kappa (κ) index.

3. Results

The study included 356 patients [70.8% male gender, median (IQR) age 39 (31-47) years, BMI 27.6 (24.4-32.5) kg/m²]. Table (2) shows the baseline characteristics of the studied patients. Of the all studied patients; according to Metavir score, liver biopsies showed that 11 patients were scored as F0 fibrosis (3 %), 245 patients were F1 (69%), 58 (16%) of our patients were F2, 34 cases (10%) were F3 and only 8 patients (2%) were scored as F4. Liver stiffness values ranged from 3.4 to 63.9 kPa (median 7.15 kPa). Figure (1) shows medians and IQR of TE values for each fibrosis stage. Figures (2, 3, 4) show ROC curves of the diagnostic accuracy of FibroScan for staging fibrosis compared with liver biopsy. The AUROCs for F2 or greater, F3 or greater and cirrhosis (F4) were 0.91 (95% CI 0.87 to 0.94), 0.95 (95% CI 0.91 to 0.99) and 0.97 (95% CI 0.96 to 0.99), respectively. ROC curve analysis identified optimal cutoff value of liver stiffness measurements as high as 9.8 kPa for $F \geq 2$, 10.4 kPa for $F \geq 3$, and 17.2 kPa for $F = 4$. The diagnostic accuracy of FibroScan confirmed its excellent accuracy, tab. (3). The overall relation between all patients on all fibrosis stages when comparing both FibroScan and biopsy was significant agreement between both (the kappa measure was 0.430 and $p<0.001$). The overall relation between all patients on all fibrosis stages when comparing both FibroScan and biopsy was significant agreement between both (the kappa measure was 0.430 and $p<0.001$), tab. (4).

Table (2) Baseline characteristics of studied patients

Characteristic	*Value*
All patients	356
Male Gender	252 (70.8%)
Age, years	39.00 (31.00-47.00)
BMI, kg/m²	27.57 (24.44-32.51)
BMI ≥ 30 kg/m²	111 (31.2%)
ALT, U/L	47.50 (32.00-69.75)
AST, U/L	38.00 (28.93-60.00)
Albumin	4.50 (4.20-4.80)
Bilirubin	0.70 (0.60-0.80)
Glucose	91.00 (84.75-102.00)
Hgb	14.00 (12.90-15.10)

WBCs	6300 (5200-7500)
Platelets	207.00 (167.00-242.00)
HCV PCR	643500 (154500-1468312)
METAVIR score	
- F0	11 (3.1%)
- F1	245 (68.8%)
- F2	58 (16.3%)
- F3	34 (9.6%)
- F4	8 (2.2%)

Data are presented as number (%) or median (IQR)
BMI, Body Mass Index; ALT, alanine transaminase; AST, aspartate transaminase; Hgb, Hemoglobin; WBCs, White Blood Cells; HCV PCR; Hepatitis C Virus Polymerase Chain Reaction

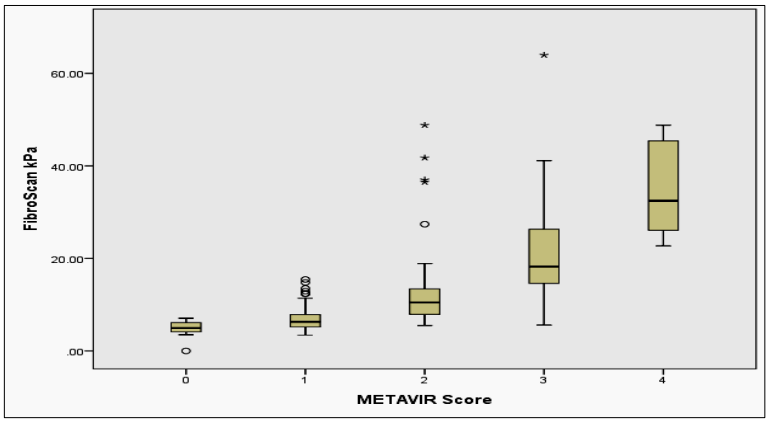

Figure (1) Box plot for TE in patients with chronic hepatitis C. Central box represents values from lower to upper quartile (25–75th percentile). Middle line represents median. Line extends from minimum to maximum value, excluding outside values which are displayed as separate points.

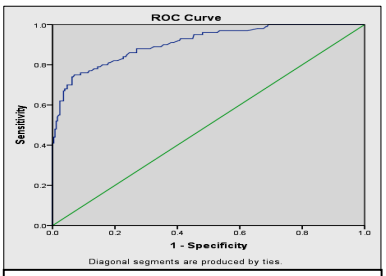

Figure (2) ROC Curve to differentiate F01 from F234

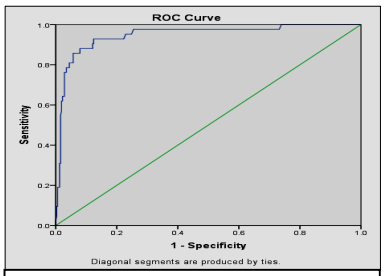

Figure (3) ROC Curve to differentiate F012 from F34

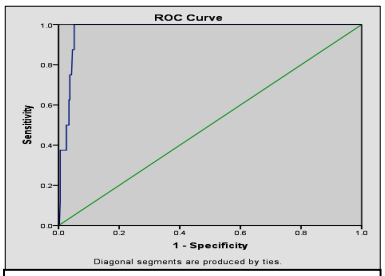

Figure (4) ROC Curve to differentiate F0123 from F4

Table (3) Diagnostic test evaluation of FibroScan and METAVIR score

--	***F ≥ 2***	***F ≥ 3***	***F = 4***
FibroScan cut off (kPa)	9.825	10.375	17.225
AUROC	0.908	0.947	0.974
P value	<0.001	<0.001	<0.001
95% CI	0.873-0.943	0.909-0.986	0.955-0.992
Sensitivity (%)	75.00	92.86	100.00
Specificity (%)	92.97	87.58	92.24

PPV (%)	80.65	50.00	22.86
NPV (%)	90.49	98.92	100.00
Accuracy (%)	87.92	88.20	92.42

The overall relation between all patients on all fibrosis stages when comparing both FibroScan and biopsy was significant agreement between both (the kappa measure was 0.430 and p<0.001).

Table (4) Degree of agreement between FibroScan and biopsy in detecting fibrosis stage

--		FibroScan				Total
		F0-1	***F2***	***F3***	***F4***	
Liver Biopsy Metavir Score	***F0-1***	238	8	10	0	256
	F2	22	7	21	8	58
	F3	3	0	12	19	34
	F4	0	0	0	8	8
	Total	263	15	43	35	356

κ = 0.430, p<0.001.

4. Discussion

In Egypt, where the HCV prevalence is the highest in the world [24], the National recommendations required that HCV-infected patients undergo a liver biopsy at the initial evaluation and that a treatment is offered to patients with a fibrosis rate ≥F2. Having a cheaper and more acceptable alternative to liver biopsy is critical in a country where six million individuals are chronically infected with HCV [25]. However, these new noninvasive methods should be locally evaluated, as circulating virus genotype (genotype 4), increased body mass index highly prevalent in Egypt, and co-infections with schistoso-miasis may interfere with liver fibrosis assessment. The national plan of action for prevention, care and treatment of viral hepatitis in Egypt (2014-2018) suggested the use of noninvasive methods (FibroScan and FIB4) for evaluation of viral hepatitis patients [26]. The use of TE is based on establishing cutoff values for each stage of fibrosis. A diagnosis of stage F ≥2, F ≥3 and F4 (cirrhosis) is based on measurements of liver stiffness that vary, according to some studies, from 6.2 to 8.8 Kpa, 7.7 to 10.8 kPa and from 11 to 16.3 kPa (Table 1). TE might be influenced by the etiology of liver disease [27] and the prevalence of fibrosis, known as spectrum effect [28]. These two major factors may explain the difference among these studies. Our major strength was the fact that our sample was composed exclusively by patients with chronic hepatitis C infection. Previous studies that have evaluated TE analyzed patients with chronic liver disease of mixed etiologies. Liver stiffness measurement accuracy and proposed cutoffs were different according to the liver disorder [29]. Although the agreement of fibrosis stages between TE and liver biopsy is good (κ = 0.430, p<0.001), however, we found discrepancies on studying the effectiveness of TE as a method for diagnosis of hepatic fibrosis compared to that of liver biopsies. In our study we found 256 patients with F0-1 on liver biopsy, and on FibroScan, 263 showed F0-1, 58 patients showed F2 on liver biopsy, while by FibroScan 15 cases were F2, 43 cases were F3 on liver

biopsy, while 34 were F3 by FibroScan. Eight patients showed F4 on liver biopsy, while 35 patients showed F4 by Fibroscan. The areas under ROC curve for the diagnosis of fibrosis F=2, F=3 and F=4 were 0.908, 0.947 and 0.974, for the cut-off values of 9.825 kPa, 10.375 kPa and 17.225 kPa. These results suggest that FibroScan performs well in identifying cases with no or minimal fibrosis, but is less accurate in identifying higher degrees of fibrosis. This is important because F2 is a threshold for initiating treatment in many counties [10]. Perazzo et al. [30] attributed this over-estimation of liver fibrosis by TE to flare of transaminases, extrahepatic cholestasis and liver congestion, non-fasting status, and liver steatosis. Wong et al. [31] concluded that TE might overestimate liver fibrosis when ALT is elevated in cases of chronic hepatitis B or C.

5. Conclusion

Transient elastography is an easy and quick clinical non-invasive method to perform and results are available immediately. It is a reliable tool for diagnosis and monitoring of liver fibrosis among patients with Chronic HCV infection It performs better in cases with no or minimal fibrosis. Hence, it could be useful in monitoring liver disease and follow up.

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